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NEW PRINCIPLES FOR TOXIC AGENT ALARMS

Final Report
covering the period
1 October 1959 to 31 January 1961

XEROX

Prepared by
Robert T. Morrison and Seymour Z. Lewin
31 May 1961
Contract No. DA-18-108-405-CML-575

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New York University
NEW PRINCIPLES FOR TOXIC AGENT ALARMS
R.T.Morrison and S.Z.Lewin

Final Report, 31 May 1961, 87 pp
Contract DA-18-108-405-CML-575

Part One: Two Experimental Approaches.
Part Two: A Study of the Practical Sensitivity Limits of Certain Trace Detection Techniques

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ERRATA

The following typographical errors occur in the Final Report entitled "New Principles for Toxic Agent Alarms," Contract No. DA-18-108-405-CML-575, New York University, May 31, 1961.

Part Two

A Study of the Practical Sensitivity Limits of Certain Trace Detection Techniques

page 32, line 4 from bottom: "It is quite convenient..."

page 34, line 6 from bottom: "...include Cl^-, Br^-, I^-, CN^-,...."

line 2 from bottom: "...graphically from a potential...."

page 36, line 2 from bottom: " ± 0.1% is obtained...."

page 37, line 1: "accuracy of ± 1.0%. This...."

line 3: "...coulombs passed is determined...."

page 39, line 4 from bottom: "...electrodeposition process, thus ...."

page 41, line 5 from bottom: "...voltage, or resistance."

page 42, line 8 from bottom: "...point, the potentials...."

page 44, line 1: "as abscissa."

line 6: "$i_d = 607\ n\ D^{1/2}\ C\ m^{2/3}\ t^{1/6}$"

line 11: "...mercury drop flowing per unit time from...."

line 6 from bottom: "..1 lambda (10^{-3} ml), since..."

page 46 line 3: "...and that $m^{2/3}\ t^{1/6} = 2.28$,...."

page 47 line 11: "SO_4^{--}"

page 48 line 9: "(macro) and 5 ml....."

line 8 from bottom: "....minimum fluorine..."

page 51 line 5 from bottom: "....rotating platinum indicator..."

page 52 line 7 from bottom: "...cobalt reported was 5.0×10^{-4} M,..."

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page 54, line 10 from bottom: "...resulted in a diffusion..."
page 56, line 8 from bottom: "No Data"
line 5 from bottom: "Phosphate"
line 1 from bottom: "Vitamin E"
page 59, line 5 from bottom: "Manganese has..."
page 62, line 7 from bottom: "...generated bromine at a..."
line 4 from bottom: "Buck, Farrington and Swift..."
line 3 from bottom: "...bromine at a current rate..."
page 63, line 2: "...bromine at a current rate..."
page 65, line 14: "...practical instrumental..."
line 16: "...taken as 1 lambda..."
line 7 from bottom: "...typical calculation..."
page 66, line 1 from bottom: "...electrolytes was..."
page 69, line 13: "substances."
page 71, line 6 from bottom: "a variable high..."
page 73, line 8: "...glacial acetic acid solution..."
page 78, line 11: "...parameter in cm^3 mv/mg..."
line 12: "...chart in cm^2, C_1..."
line 8 from bottom: "...micrograms/microliter (62)).
page 79, line 7: "...detection possible with..."
page 81, line 5: "...potential changes that..."
line 6 from bottom: "...However, the techniques..."
line 2 from bottom: "...for the detection of small..."
page 82, line 1: "changes in a flowing gas."
line 6 from bottom: "...from the ends of two..."
page 84, line 4: "...presence of other constituents (70)."
page 85, line 4: "efficiency of the source of..."

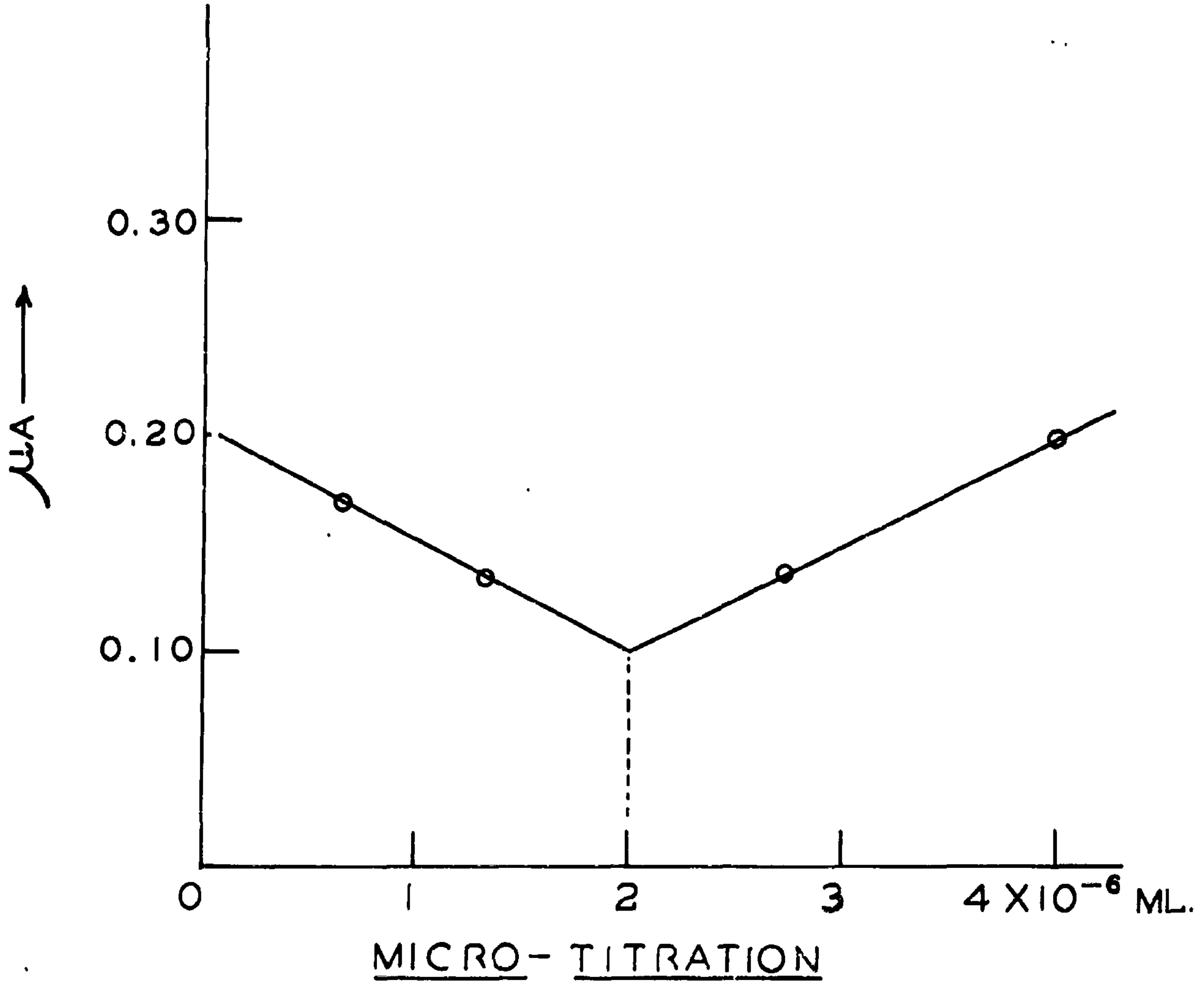


FIG. 1

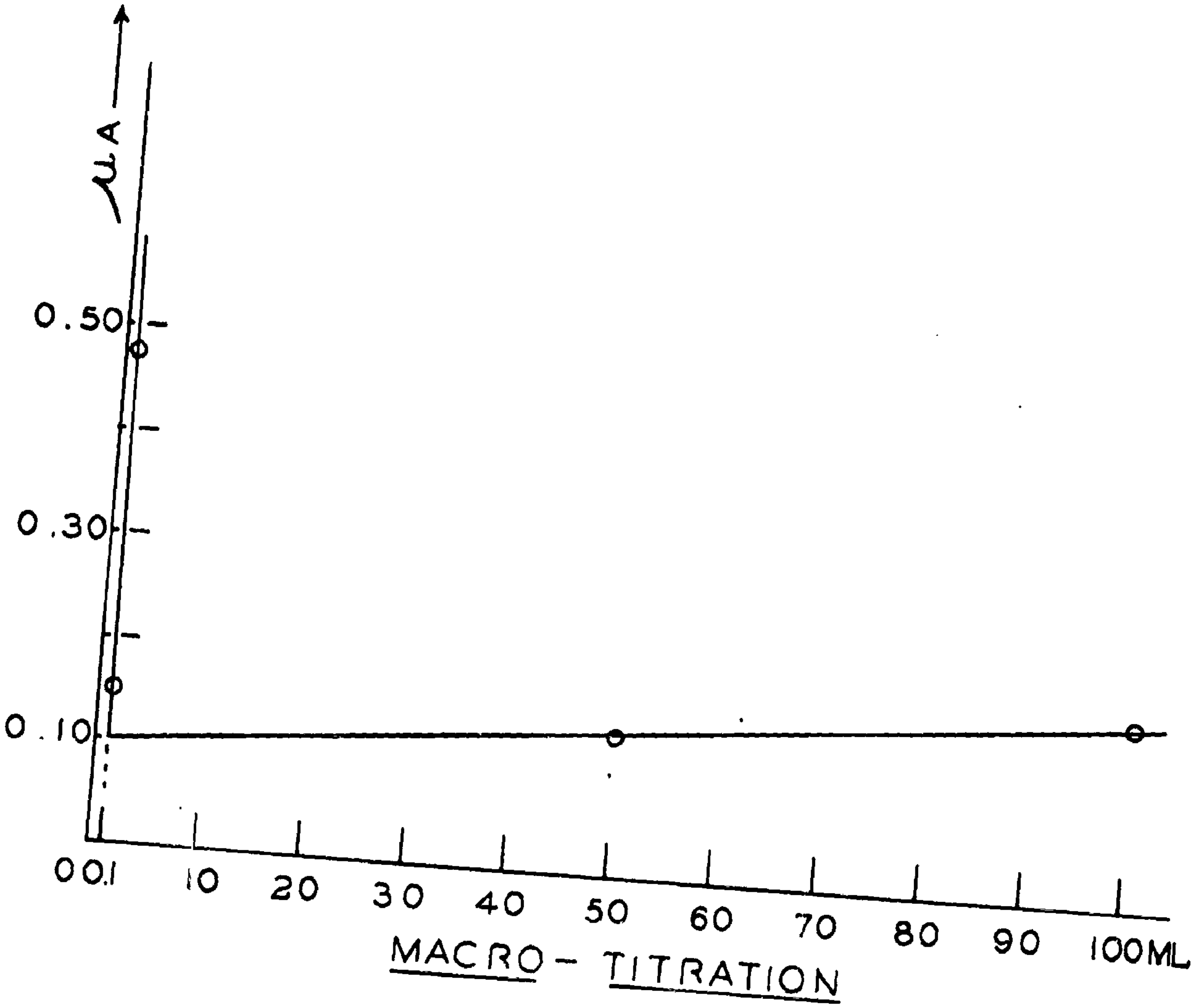
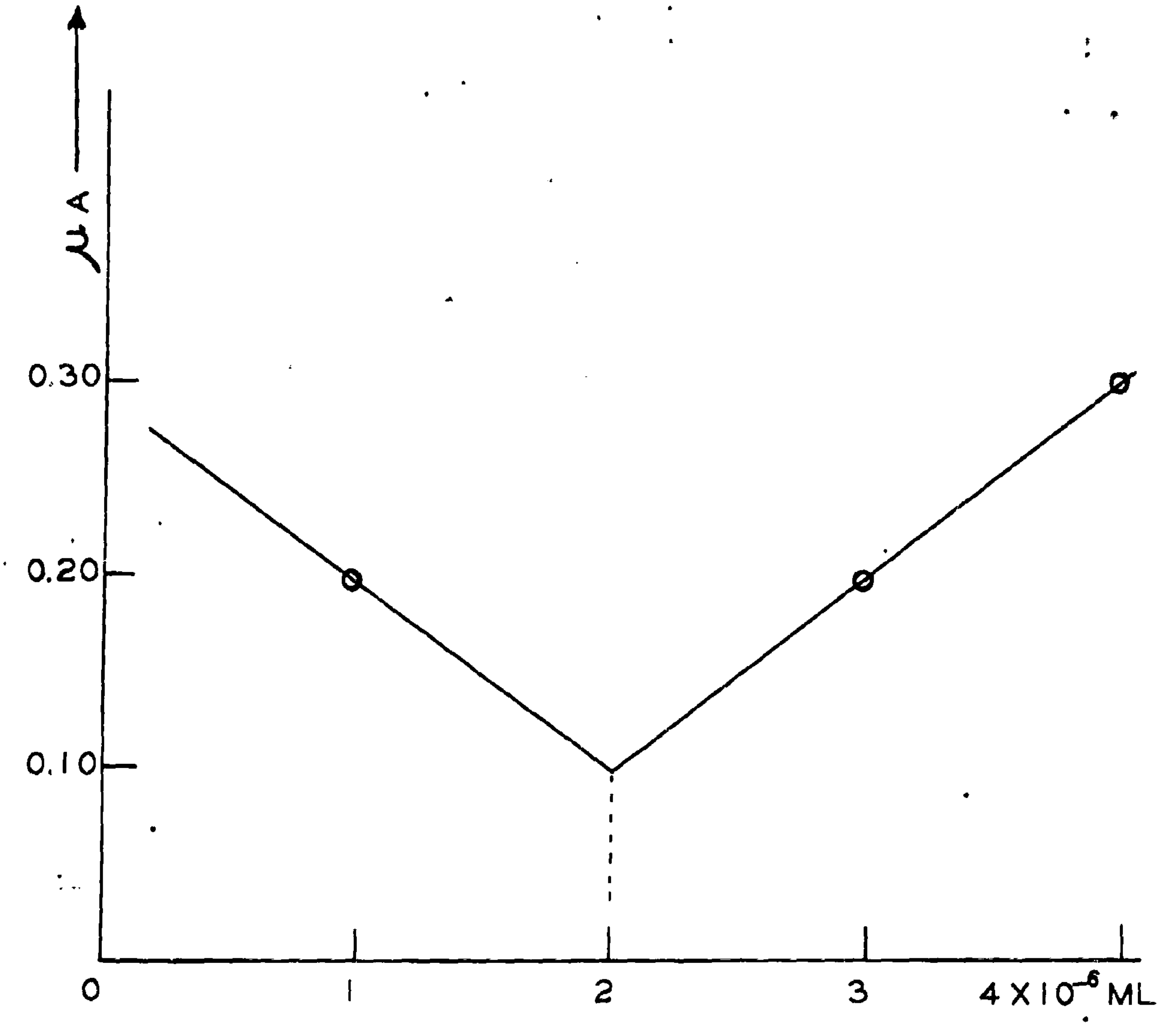

μA
0.50
0.30
0.10
0 0.1
10
20
30
40
50
60
70
80
90
100ML
MACRO- TITRATION

FIG. 2



MICRO - TITRATION

FIG. 3

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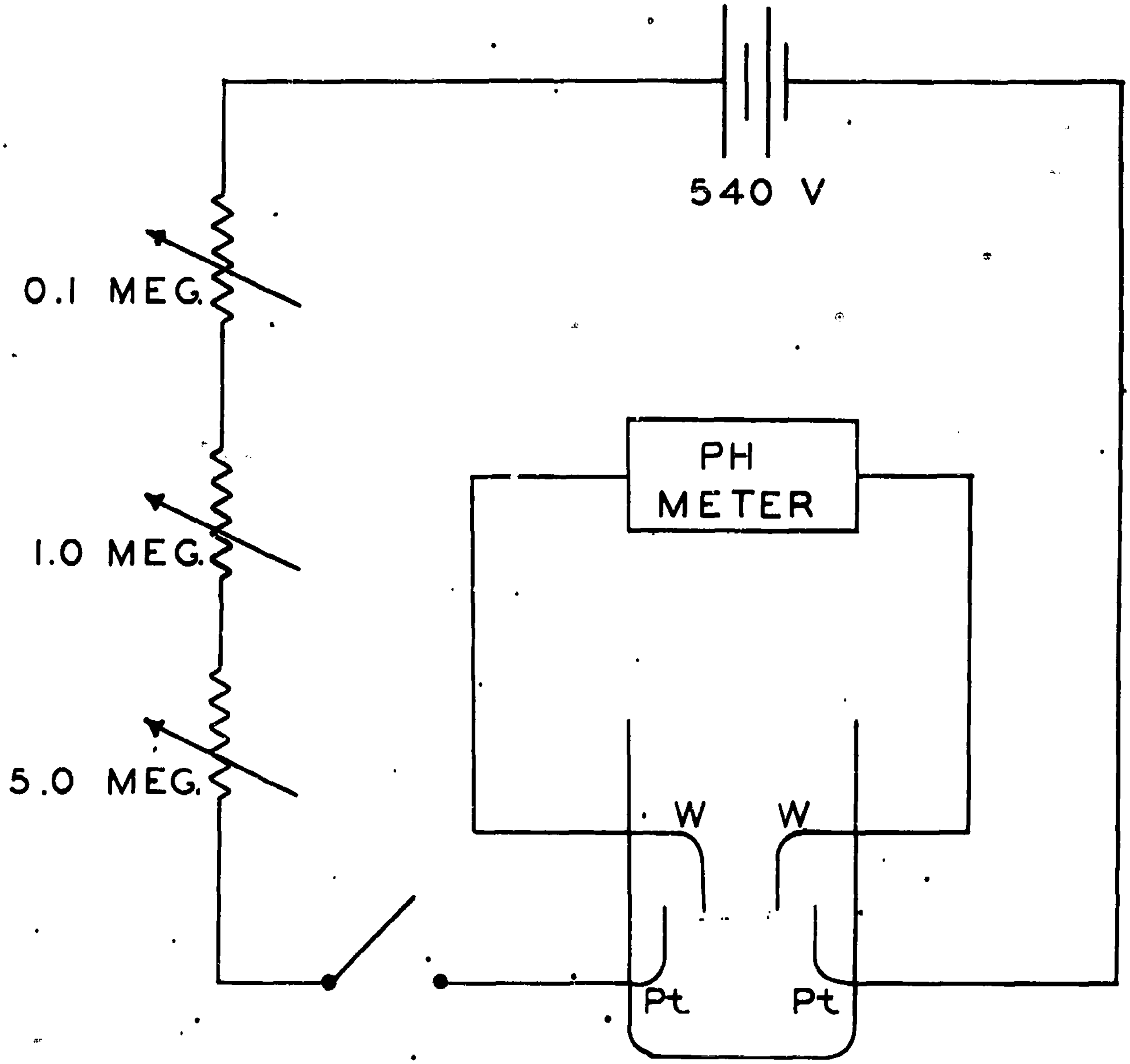
540 V
0.1 MEG.
1.0 MEG.
5.0 MEG.
PH METER
W
W
Pt
Pt

D.C. CONDUCTANCE

FIG. 4

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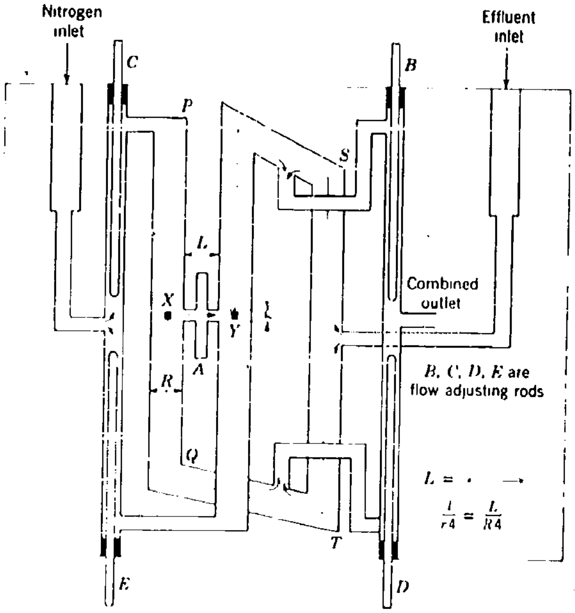
Nitrogen inlet
C
P
S
B
Effluent inlet
L
X
Y
A
R
Q
Combined outlet
B, C, D, E are flow adjusting rods
L =
$\frac{l}{r4} = \frac{L}{R4}$
T
E
D

FIGURE 5. GAS DENSITY BALANCE

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PART ONE.

TWO CHEMICAL APPROACHES

by

Robert T. Morrison

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CATALYSIS OF NUCLEOPHILIC CLEAVAGE OF PHOSPHONATES

Introduction

A suitable alarm for toxic agents should be based on chemical properties characteristic of the broad class of phosphonates, i.e., compounds containing the RPO grouping. The most widely studied group of reactions undergone by these compounds is nucleophilic cleavage (1), where Z is any neutral or negatively charged base. To be adaptable

$$(1) \qquad :Z + RP(O)(OR')X \longrightarrow RP(O)(OR')Z + X^-$$

to the detection of phosphonates, nucleophilic cleavage must be used in a way that reveals a difference between phosphonates and other compounds likely to be encountered. At least two important differences are known: (a) the high oxidizing power of peroxyphosphorus compounds, and (b) the low basicity of phosphonate anions (or the equivalent, the high acidity of phosphonic acids).

The unusual oxidizing power of peroxyphosphorus compounds is the basis of the Schoenemann reaction[1], in which the nucleophilic reagent, Z, is the perhydroxide ion, OOH^-.

The low basicity of phosphonate anions permits phosphonates to catalyze the Lossen rearrangement of hydroxamic acids[2]. Here Z is the hydroxamate anion, as shown in (1a). The speed of Lossen rearrangement

$$(1a)\quad R''\text{-}CO\text{-}NHO^- + RP(O)(OR')X \longrightarrow X^- \quad \underset{\text{I}}{RP(O)(OR')O\text{-}NH\text{-}CO\text{-}R''}$$

$$(2)\quad \text{I} \quad \text{base} \longrightarrow \underset{\text{II}}{RP(O)(OR')O\text{-}N\text{-}CO\text{-}R''^-}$$

$$(3)\quad \text{II} \longrightarrow \underset{\text{III}}{RP(O)(OR')O^-} \quad RNCO \longrightarrow \text{rearrangement products}$$

depends on the rate of (3), which in turn depends inversely on the basicity of the anion being formed[3], in this case the weakly basic phosphonate anion, III.

One could visualize a simpler reaction in which the low basicity of this anion could be taken advantage of: hydrolysis of a phosphonate in the presence of (and catalyzed by) a neutral base, e. g., a tertiary amine (4). Occurrence of such a reaction might be detected by an in-

$$(4)\quad RP(O)(OR')X + :B + H_2O \longrightarrow RP(O)(OR')O^-B^+ + HX$$

crease in conductivity of the solution[4]. Phosphonates are unusual in being neutral compounds that on hydrolysis yield strong acids; neutralization of the strong acids by even weak bases generates ions.

The limiting aspect of any approach based on nucleophilic cleavage of phosphonates is the rate at which the initial attack (1) occurs. One of the major difficulties in finding an alarm suitable for all agents is the fact that some agents may be less reactive toward nucleophilic cleavage than are G-agents, due chiefly to change in the nature of the group, X, being displaced.

Considerable evidence suggests that nucleophilic cleavage of phosphonates and related compounds can, in general, be catalyzed by acids (in particular metal ions), bases, and combinations of acids and bases: metal ions and chelates catalyze hydrolysis of diisopropyl phosphonofluoridate and related compounds[5,6]; lanthanum hydroxide gel catalyzes hydrolysis of phosphates[7]; calcium and magnesium ions catalyze solvolysis of pyrophosphates, as do also tertiary amines like lutidines and collidines[8]. One of the most striking examples is the 100,000-fold increase in rate of solvolysis of a pyrophosphate caused by a combination of calcium ion and 2,6-lutidine[8].

Plan

We planned to study in a systematic way the catalysis of nucleophilic cleavage of phosphonates by acids, bases, and combinations of the two. If we learned how to speed up cleavage of phosphonates in general, this knowledge could be used to extend colorimetric methods, like the Schoenemann reaction or rearrangement of hydroxamic acids, to the detection of less reactive agents, and to develop new methods, like the conductometric method mentioned above.

So that a large number of catalysts and catalyst-combinations could be studied rapidly and exactly, we planned to use a reaction whose rate could be followed easily: hydrolysis of a simple compound like diethyl methylphosphonate, $CH_3PO(OC_2H_5)_2$. Hydrolysis of this compound was known to occur at a convenient rate[9], and could be followed titrimetrically[9] or, perhaps more conveniently, by a spectrophotometric method[10]. It has the simple, basic phosphonate structure, and is not particularly reactive; consequently, results obtained using it should indicate behavior to be expected of most phosphonates, not just a few unusual ones. Results observed for hydrolysis, in which water or hydroxide ion is the nucleophile (Z), should be applicable to attack by more complicated nucleophiles.

We planned to work out a method of following hydrolysis in alkaline solution, rather than in acidic solution, because it is faster[9], simpler to follow (stopping at the monoethoxy stage), and more generally applicable to solutions where, for example, hydroxamate or perhydroxide ions must be generated.

We then planned to measure the rates of hydrolysis in solutions containing (a) various metal ions or chelates, (b) various neutral bases, especially tertiary amines, (c) combinations of metal ions and bases, and (d) compounds containing both acidic and basic groups in the same molecule[11].

Results

Preparation of Diethyl Methylphosphonate.--This compound (IV) was selected for the cleavage studies as described above, and was prepared by the Arbuzov reaction (5) as described by Hudson and Keay[9] and Ford-Moore and Williams[12].

(5) $P(OC_2H_5)_3$ CH_3I $CH_3PO(OC_2H_5)_2$ C_2H_5I

IV

Triethyl phosphite (55 g, 0.33 mole) was refluxed for two hrs. with a slight excess of methyl iodide (50 g, 0.35 mole). Upon distillation at atmospheric pressure the theorectical amount of ethyl iodide (51.1 g, 0.33 mole) was collected at 61-86°. Vacuum distillation gave diethyl methylphosphonate, wt. 33.6 g (67% yield) b.p. 59-62.5° (2.5 mm), n_D^{16} 1.4145. Distillation through an efficient fractionation column gave material of b.p. 52-54.5° (1 mm), n_D^{16} 1.4143 (lit.[12] b.p. 64-65° at 2 mm, n_D^{16} 1.412).

The infrared spectrum of the ester was taken and found to correspond exactly to the spectrum reported[13] for diethyl methylphosphonate. Comparison with the spectrum of triethyl phosphite indicated the absence, within the limits of the analysis, of the latter compound.

Attempted Spectrophotometric Method for Kinetics of Alkaline Hydrolysis.-- The next stage was to work out a method for following the kinetics of alkaline hydrolysis of diethyl methylphosphonate. It was hoped that hydrolysis could be followed by measurement of an increase in optical density in the ultraviolet region. Such a method would be fast and accurate, since hydrolysis could be carried out in the spectrophotometric cell itself with no need for withdrawal of samples.

The method would require a significant difference in absorption between the ester and its hydrolysis product, $CH_3P(O)(OC_2H_5)O^-$, in solutions of a concentration (.01-.05M) at which hydrolysis proceeds at a reasonable rate[9]. The spectrum of the more strongly absorbing species, the hydrolysis products, was measured in the following way.

A .05M solution of diethyl methylphosphonate in .1N sodium hydroxide was heated at 80° for one hr., conditions which are known[9] to cause complete hydrolysis. The resulting solution, placed in a Beckman DU Spectrophotometer, showed no detectable absorption in the range 220-340 m .

A .5M solution of diethyl methylphosphonate in 1N sodium hydroxide was treated similarly. The data obtained are given in Table I.

TABLE I

ULTRAVIOLET SPECTRUM[a] OF ALKALINE HYDROLYSIS PRODUCTS OF DIETHYL METHYLPHOSPHONATE[b]

Wavelength, m	Optical density
222	1.975
224	1.382
226	1.013
228	.874
232	.508
236	.392
240	.333
244	.299
252	.261
260	.231
270	.207
280	.188
290	.168
300	.149
320	.116
340	.094

(a) Light path, 1 cm; slit width, 0.8.

(b) Original concentrations: NaOH, 1N; ester, 0.5M.

Our experience[14] has shown that data collected at wavelengths below about 265 m are not reliable for kinetics purposes, perhaps because of dissolved oxygen. As can be seen, the absorption above 265 m is quite weak, even for the concentrated solution used. It was therefore decided to abandon the spectrophotometric approach to the measurement of the kinetics.

Titrimetric Method for Kinetics of Alkaline Hydrolysis.--A titrimetric method similar to that described by Hudson and Keay[9] was next worked out.

Hydrolysis was carried out in a 100-ml volumetric flask suspended in a constant-temperature bath heated to 60.0° 0.1°. About 85 ml of water was added to the flask and allowed to equilibrate. A sample of ester (about .3 g) to make an approximately .02M solution was weighed out and washed into the flask with temperature-equilibrated water. A 5-ml portion of 1N sodium hydroxide, previously brought to temperature, was then introduced, and water was added to the mark.

At intervals 5-ml aliquots were withdrawn. Each was delivered into a 10-ml beaker cooled in ice-water and containing phenolphthalein and a micromagnetic stirring bar. The solution was titrated under nitrogen with standard .07N potassium hydrogen phthalate solution. Titration was complete within 3 min. of withdrawing the sample.

The second-order constant, k, was calculated using the equation

$$k = 2.303/tNn \qquad \log (n_o - n\ \ )/n_o \qquad \log n_t/(n_t - n\ \ )$$

where t is time in min., N is normality of the acid, and n_o, n_t, and n are volumes of acid required.

Tables II, III, and IV (pp. 9 and 10) show results of satisfactory runs (Table II by one assistant, and Tables III and IV by another). The rate constants obtained, 13.6, 12.7, and 13.3 (liters moles^{-1} min^{-1} x 10^5) agree fairly well with the value of 15.6 found by Hudson and Keay[9].

TABLE II

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60°

t, min.	n, ml	k, liters moles^{-1} min^{-1} x 10^5
0	3.525	----
22	3.329	13.9
30	3.270	14.1
40	3.213	13.1
50	3.125	14.2
60	3.103	12.7
65	3.055	13.4
75	2.983	14.1
90	2.919	13.8
120	2.800	13.5
135	2.747	13.5
150	2.702	13.4
180	2.619	13.4
1620	2.094	----
		13.6

TABLE III

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60°

t, min	n, ml	k, liters $moles^{-1}$ min^{-1} x 10^5
0	3.500	——
12	3.260	13.4
19	3.161	13.1
24	3.079	12.7
30	2.998	12.2
36	2.921	12.1
42	2.817	13.0
50	2.741	12.4
53	2.676	13.0
60	2.602	12.9
75	2.455	12.8
90	2.319	12.7
120	2.093	12.8
181	1.765	12.6
240	1.540	12.4
		12.7

TABLE IV

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60°

t, min	n, ml	k, liters $moles^{-1}$ min^{-1} x 10^5
0	3.500	----
18	3.084	15.7
24	3.001	14.9
30	2.998	11.9
36	2.891	12.7
42	2.786	13.6
48	2.701	13.4
54	2.598	13.9
60	2.600	12.6
71	2.485	12.6
90	2.296	12.7
120	2.041	13.2
150	1.874	13.0
200	1.617	13.1
264	1.389	13.2
		13.3

Effect of Pyridine on Alkaline Hydrolysis.--As described above, hydrolysis is followed by withdrawal of aliquots from the alkaline reaction mixture and titration of these with standard acid. As reaction proceeds, hydroxide is consumed and the titer of the aliquots decreases. The presence of an amine complicates the measurement of hydroxide ion concentration.

For the very weakly basic amine pyridine (pK_b ca. 9), it was found that titration with phenolphthalein as indicator gives satisfactory results. Under these conditions, pyridine is not titrated at all, and the entire titer is due to hydroxide ion.

Tables V and VI (pp. 12) summarize results obtained for hydrolysis of diethyl methylphosphonate in the presence of pyridine. As in the control runs, the initial concentration of hydroxide ion was 0.05M and of ester 0.02 to 0.05M. The concentration of pyridine was 0.02M. The rate constants obtained, 12.3 and 12.5 (liter moles^{-1} min^{-1} x 10^5) are not significantly different from those obtained in the absence of amine (12.7 - 13.6) and show that pyridine does not catalyze the hydrolysis.

TABLE. V

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60° IN THE PRESENCE OF PYRIDINE

t, min	n, ml	k, liter moles^{-1} min^{-1} x 10^5
0	3.570	----
13	3.268	13.0
24	3.095	11.6
30	2.990	11.8
36	2.883	12.0
42	2.790	12.1
48	2.710	11.9
54	2.608	12.4
60	2.525	12.5
76	2.350	12.2
94	2.151	12.5
120	1.918	12.7
180	1.572	12.4
		12.3

TABLE VI

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60° IN THE PRESENCE OF PYRIDINE

t, min	n, ml	k, liters moles^{-1} min^{-1} x 10^5
0	3.570	----
12	3.319	12.8
18	3.218	12.8
24	2.094	12.8
33	2.972	11.4
36	2.913	12.5
42	2.814	12.8
48	2.717	12.8
54	2.654	12.1
60	2.576	12.1
75	2.403	11.9
91	2.266	13.9
120	2.016	12.2
185	1.631	12.7
240	1.431	12.3
		12.5

Effect of Triethanolamine on Alkaline Hydrolysis.--For more strongly basic amines like trialkylamines (pK_b ca. 3), it was found that titration with a strong acid (instead of acid phthalate) and methyl red as indicator gives satisfactory results. Under these conditions, the amine is titrated quantitatively, and the total titer is that of hydroxide ion plus that of amine. The amine titer is known from the quantity of amine added, and remains constant throughout a run; it can be substracted from the total titer. Anticipating the study of heavy metal ions and their solubility requirements, nitric acid was selected as titrating acid.

Triethylamine, (b.p. 89°) was found to be too volatile at the temperature of hydrolysis (60°) for study of its catalylic effect. Tri-n-propylamine was sufficiently non-volatile but not soluble enough in water for the desired concentration (ca. 0.02M) to be reached. Triethanolamine was finally selected as having the required basicity, non-volatility, and solubility.

Tables VII and VIII (p. 15) summarize the results obtained when diethylmethylphosphonate was hydrolyzed in the presence of triethanolamine. The initial concentrations were: hydroxide ion, 0.05M; ester, 0.02M; triethanolamine, 0.02M. The titer of hydroxide ion, n, was obtained by subtracting from the experimentally measured titer, n_e, the amine titer, which was known from the quantity of amine added.

The rate constants obtained, 12.2 and 11.1 (liters $moles^{-1}$ $min.^{-1}$ x 10^5) are not significantly different from those obtained in the absence of amine, 12.7 - 13.6, and show that triethanolamine does not catalyze the hydrolysis.

TABLE VII

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60° IN THE PRESENCE OF TRIETHANOLAMINE

t, min	n_e, ml	n, ml	k, liters moles^{-1} min^{-1} x 10^5
0	5.000	3.589	----
14	4.755	3.344	21.2
19	4.742	3.331	16.6
30	4.700	3.289	12.5
37	4.639	3.228	12.5
42	4.587	3.176	12.9
48	4.561	3.150	12.2
54	4.526	3.115	11.9
60	4.456	3.045	12.8
76	4.365	2.954	12.4
90	4.305	2.894	11.9
121	4.137	2.726	12.1
155	4.018	2.607	11.2
191	3.903	2.492	11.7
			12.2

TABLE VIII

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60° IN THE PRESENCE OF TRIETHANOLAMINE

t, min	n_e, ml	n, ml	k, liters moles^{-1} min^{-1} x 10^5
0	5.000	3.589	----
7	4.899	3.488	17.1
12	4.897	3.486	10.7
18	4.853	3.442	10.6
24	4.829	3.418	9.3
30	4.809	3.398	8.5
36	4.726	3.315	10.6
42	4.675	3.264	11.0
48	4.640	3.229	10.9
54	4.594	3.183	11.2
60	4.562	3.151	11.1
75	4.474	3.063	11.2
90	4.389	2.978	11.4
120	4.266	2.855	11.0
160	4.118	2.707	11.2
			11.1

Effect of Heavy Metal Complexes.--First, experiments were carried out to determine the solubility of various heavy metal ions complexed with various amines in a medium similar to the hydrolysis medium. The ions tested were silver, mercuric, and cupric, and the complexing agents used were pyridine, triethanolamine, and alpha,alpha'-bipyridyl. Of the possible combinations only the bipyridyl complexes of cupric and mercuric ions did not give heavy precipitates. Of these two, only the cupric ion remained entirely in solution, and this only when the bipyridyl:cupric ion ratio was 2.5:1.

Hydrolysis of diethyl methylphosphonate (initial concentration 0.02M) in sodium hydroxide (initial concentration 0.05M) in the presence of cupric ion (0.01M) and alpha,alpha'-bipyridyl (0.025M) was carried out. Tables IX and X (pp. 17 and 18) summarize the results obtained.

As can be seen, the "constant" decreases as reaction proceeds, and tends to level off at a value quite close to that observed for the uncatalyzed hydrolysis. Whatever the cause of the more rapid consumption of base at the beginning of the reaction, it appears that hydrolysis is not catalyzed markedly by the heavy metal complex.

TABLE IX

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60° IN THE PRESENCE OF CUPRIC ION

t, min	n, ml	k, liters $moles^{-1}$ min^{-1} x 10^5
0	3.750	----
4	3.388	174
8	3.345	97.4
17	3.127	41.0
24	3.254	45.3
30	3.016	61.0
36	3.227	24.4
42	3.216	26.6
48	3.211	23.5
54	3.180	21.4
60	3.206	19.1
70	3.153	19.5
85	3.136	16.4
120	3.014	15.2
147	2.942	14.8
165	2.905	14.3
180	2.907	13.0
210	2.826	13.4

TABLE X

ALKALINE HYDROLYSIS OF DIETHYL METHYLPHOSPHONATE AT 60° IN THE PRESENCE OF CUPRIC ION

t, min	n, ml	k, liters moles^{-1} min^{-1} x 10^5
0	3.750	----
6	3.370	89.5
12	3.361	29.2
18	3.300	36.6
24	3.212	34.5
30	3.208	27.9
36	3.185	24.5
42	3.178	21.4
48	3.147	20.1
53	3.125	19.0
60	3.097	18.0
75	3.095	14.5
90	2.945	16.3
122	2.878	14.4
165	2.771	12.3
195	2.707	11.7
240	2.636	10.5

Future Work

Although only two amines and one heavy metal ion complex were studied, the results do not encourage further study, at least in the present system. It may very well be that the ideas of catalysis by bases and acids are valid, for the reasons given in the Introduction, but that neither kind of catalysis is readily observable for the reaction studied here, where the attacking nucleophile is hydroxide ion.

Hydroxide is a powerful enough nucleophile that it may obscure any attack by an amine; even though the latter may have a high nucleophilicity:basicity ratio, its net nucleophilic power may be lower than that of hydroxide.

For solubility reasons, the use of hydroxide ion requires rather tight complexing of the heavy metal ion, and such complexing may prevent the metal ion from displaying its acidic properties, at least for a reaction that proceeds as readily, without catalysis, as the present one.

For the above reasons, it may be that catalysis by amines and/or metal ions can best be studied in a system where the nucleophile is less reactive or less basic than hydroxide ion. Furthermore, it might be most profitable to carry out such a study only when such a specific system suggests itself as one which, for other reasons, would be a suitable basis for an alarm.

REARRANGEMENT OF HYDROXAMIC ACIDS

Introduction

Among the reagents that cause rearrangement of hydroxamic acids are G-agents[15] and other toxic agents[16]. In these cases, reaction presumably involves[17] reactions (1) to (5).

(1) $$\underset{\text{I}}{\text{R-CO-NHOH}} + \text{OH}^- \rightleftharpoons \text{H}_2\text{O} + \text{R-CO-NHO}^-$$

(2) $$\text{R-CO-NHO}^- + \text{R'P(O)(OR'')X} \longrightarrow \text{X}^- \quad \underset{\text{II}}{\text{R'P(O)(OR'')O-NH-COR}}$$

(3) $$\text{II} + \text{OH}^- \rightleftharpoons \text{H}_2\text{O} \quad \underset{\text{III}}{\text{R'P(O)(OR'')O-N-COR}^-}$$

(4) $$\text{III} \longrightarrow \text{R'P(O)(OR'')O}^- \quad \text{RNCO}$$

(5a) $$\text{RNCO} + \text{H}_2\text{O} \longrightarrow \underset{\text{IV}}{\text{RNH}_2}$$

(5b) $$\text{RNCO} + \text{R-CO-NHOH} \longrightarrow \underset{\text{V}}{\text{R-NH-CO-ONH-CO-R}}$$

A possible basis for an alarm would be a change in color in proceding from the hydroxamic acid (I) to its rearrangement product (IV or V). Such a color change might be produced with hydroxamic acids in which group R (in I) is an arylazo group. The simplest example is p-(phenylazo)-benzohydroxamic acid (VI).

$$(6)\quad \underset{\text{VI}}{C_6H_5{-}N{=}N{-}C_6H_4{-}CO{-}NHOH{-}p} \longrightarrow \underset{\text{VII}}{C_6H_5{-}N{=}N{-}C_6H_4{-}NH_2{-}p}$$

$$\text{or}\quad \underset{\text{VIII}}{C_6H_5{-}N{=}N{-}C_6H_4{-}NH{-}CO{-}ONH{-}CO{-}R}$$

Examination of the spectra reported[18] for a number of azo compounds shows that, in general, electron-withdrawing substituents (e.g., carbonyl, nitro, or, presumably, -CO-NHOH) have little effect on the visible spectrum of the compound, whereas electron-releasing substituents (e.g., amino, acetamido, or, presumably, -NH-CO-ONH-COR) shift the intense absorption bands toward longer wavelengths. Compare, for example: azaobenzene, 3200 A; p-nitroazaobenzene, 3330 A; p-dimethylaminoazaobenzene, 4100 A; p-acetamidoazobenzene, 3490 A.

On this basis, one might expect the conversion of VI into VII to be accompanied by a shift of about 800-1000 A, and conversion of VI into VIII by a shift of 400-500 A.

If the structure of the hydroxamic acid were further modified to IX, the shift in spectrum accompanying rearrangement should be even greater,

$$\underset{\text{IX}}{p{-}NO_2{-}C_6H_4{-}N{=}N{-}C_6H_4{-}CO{-}NHOH}$$

due to interaction between the nitro group and the amino (or amido) group in the product.

Plan

We planned to prepare the hydroxamic acids VI and IX, and to measure their visible and ultraviolet spectra and the spectra of their rearrangement products. If the results bore out the hypothesis outlined above, then we would consider further modifications in structure, aimed not only at enhancing the color change, but also at increasing reactivity toward agents.

The most promising synthetic route to hydroxamic acids of this type appears to involve condensation of methyl p-aminobenzoate with various nitroso compounds[5], followed by conversion of the esters thus obtained into hydroxamic acids by treatment with hydroxylamine[6].

Results

After some work had been done, this approach was almost completely discontinued, on the advice of the Project Officer, so that effort could be concentrated on the catalysis of nucleophilic cleavage of phosphonates. The incompleted work is summarized below.

Preparation of p-(Phenylazo)benzohydroxamic Acid.--This substance (XII), a new compound, was prepared from the commercially available acid chloride (IX) by route (7)-(9).

$$(7)\quad \underset{\text{IX}}{p\text{-}C_6H_5\text{-}N{=}N\text{-}C_6H_4\text{-}COCl} + CH_3OH \longrightarrow \underset{\text{X}}{p\text{-}C_6H_5\text{-}N{=}N\text{-}C_6H_4\text{-}COOCH_3}$$

$$(8)\quad \text{X} + NH_2OH + KOH \longrightarrow \underset{\text{XI}}{p\text{-}C_6H_5\text{-}N{=}N\text{-}C_6H_4\text{-}CONHOK}$$

$$(9)\quad \text{XI} + CH_3COOH \longrightarrow \underset{\text{XII}}{p\text{-}C_6H_5\text{-}N{=}N\text{-}C_6H_4\text{-}CONHOH}$$

To the acid chloride IX (10.0 g, 0.041 mole) dissolved in 400 ml dry benzene was added 8.2 ml methyl alcohol and 28 ml triethylamine. After refluxing 45 min. the reaction mixture was cooled and filtered free of triethylammonium chloride. The benzene solution was washed with four 125-ml portions of 5% sodium carbonate solution and three 200-ml portions of water, and dried over sodium sulfate. Evaporation of the solvent gave 9.2 g (93% yield) of red-orange crystals of methyl p-(phenylazo)benzoate, m.p. 130-133° (lit.[21] 123-124°), which was used in the next step without further purification.

The hydroxamic acid XII was prepared by an adaptation of the method[20] used for the preparation of benzohydoxamic acid. To a solution of hydroxylamine in 420 ml of methanol (prepared as described[20] from 52.4 g of hydroxylamine hydrochloride and 56.1 g of potassium hydroxide) was added 9.2 g (0.038 mole) of crude methyl p-(phenylazo)benzoate, not all of which dissolved. The mixture was stirred at room temperature for 48 hrs. The red-orange precipitate, presumably the potassium salt XI, was collected on a filter and dried. Wt. 6.4 g (65% yield based on ester). Concentration of the filtrate yielded a second crop (4.3 g) of crystals, which were combined with the first crop.

To the dry crude potassium salt (10.7 g) was added 31 ml of 1.25N acetic acid solution, and the mixture was heated on a hot plate for 5 min. Water (65 ml) was added gradually and the mixture was cooled in ice. Red-orange crystals, presumably the hydroxamic acid XII, were collected on a filter, washed with water, and dried. Wt. 8.7 g (89% yield based on ester). This was recrystallized with charcoal treatment from ethyl acetate. (Much of the crude material did not dissolve, indicating that it was quite impure). Yield of recrystallized material, 4.1 g (42% based on the ester), m.p. 185-187°. Two additional recrystallizations from ethyl acetate gave material of m.p. 189.5-191.5°.

Anal. Calcd. for $C_{13}H_{11}O_2N_3$: C, 64.72; H, 4.60; N, 17.46.
Found: C, 64.57; H, 4.61; N, 18.08.

Attempts to measure the neutralization equivalent by the usual method[21] failed because the strong color of the hydroxamic acid obscured that of the trinitrobenzene indicator. Potentiometric titration was not attempted because of the low water solubility of the compound.

At this point, work on this aspect of the problem was dropped.

Preparation of p-(p-Nitrophenylazo)benzohydroxamic Acid.--It was planned to prepare this compound (XIV) from the ester XIII by reaction with hydroxylamine as described above for the preparation of p-(phenylazo)benzohydroxamic acid. The ester was to be prepared by condensation[19] of methyl p-aminobenzoate with p-nitronitrosobenzene (1).

$$(10) \quad p\text{-}NO_2\text{-}C_6H_4\text{-}NO + p\text{-}NH_2\text{-}C_6H_4\text{-}COOCH_3 \longrightarrow \underset{\text{XIII}}{p\text{-}NO_2\text{-}C_6H_4\text{-}N{=}N\text{-}C_6H_4\text{-}COOCH_3\text{-}p}$$

$$(11) \quad I + NH_2OH \longrightarrow \underset{\text{XIV}}{p\text{-}NO_2\text{-}C_6H_4\text{-}N{=}N\text{-}C_6H_4\text{-}CONHOH\text{-}p}$$

Repeated attempts to prepare p-nitronitrosobenzene in reasonable amounts failed. These included the attempted oxidation of p-nitroaniline by Caro's acid[22,23] and by peroxyacetic acid[24] under a variety of conditions; the chief product in every case was p-dinitrobenzene, a very small yield of p-nitronitrosobenzene being obtained by use of peroxyacetic acid. Attempted reduction of p-dinitrobenzene by the method of Meisenheimer[25] also failed.

As an alternative route to XIV, nitration of p-(phenylazo) benzohydroxamic acid (above) was attempted, using a method similar to that reported[26] for the nitration of $C_6H_5\text{-}N{=}N\text{-}CONHOH$.

p-(Phenylazo)benohydroxamic acid (0.455 g, 0.019 mole) was placed in a 30-ml beaker, and to it was added dropwise during about 2 min. 90% nitric acid (d. 1.50, 0.88 ml). The reaction mixture was brought to dryness by heating for 20 min. on the steam bath. The dark residue was taken up in ice-water and collected on a filter. Extraction of the dark orange-brown residue with hot ethyl acetate gave material, also dark, which after recrystallization from ethyl acetate had m.p. 286.5-289°.

Work was discontinued at this point.

Future Work

Whether or not this line should be pursued further would depend on a number of factors, especially the degree of importance assigned to colorimetric methods based on stoichiometric reactions as the basis for a highly sensitive alarm. If it were decided to continue work in this area, there still remains the question as to whether the hydroxamic acid reaction can be catalyzed to permit a rapid response to a wide variety of agents.

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PART TWO.

A STUDY OF THE PRACTICAL SENSITIVITY LIMITS OF CERTAIN TRACE DETECTION TECHNIQUES

by

Seymour Z. Lewin

I. Scope of This Report

The search for detection techniques for trace concentrations of contaminants in the atmosphere is, and will continue to be, a pressing problem. Solutions to this problem are never final solutions, for new contaminants continually come to the fore, and ever lower concentration limits become of significance. The problems of the Chemical Corps are particularly difficult in this respect, because of the special requirements of speed, accuracy, specificity, and portability in addition to the continual need for detection systems for new types of chemical agents.

In considering the types of detection techniques that could be exploited to solve these problems, it is important to be alert to the practical sensitivity limits of the various potentially available methods. That is, each of the detection techniques is limited, in practical terms, by one of the following factors:

(1) Signal-to-noise ratio

(2) Sensitivity of electronic or optical components

(3) Interference of background signals.

Some of the detection techniques in current use for certain of the chemical agents are limited by the first factor above, viz., by the fact that the inherent, irreducible noise level characteristic of ambient temperatures and well-designed electrical and optical circuitry is comparable with the signal from the atmospheric contaminant at the specified minimum concentration level. With these techniques, it is pointless to seek to push the method to still lower concentration levels.

There are certain detection techniques which are not now being routinely utilized for field detection, and which have potentially very favorable sensitivity limits. These techniques may not, at this time, be easily applied to the detection problems of the Chemical Corps because of insufficient specificity (i.e., detectability of a given chemical agent is limited by factor (3) above,) or for other reasons. But it is in the field of these techniques that the greatest range of increased sensitivities may possibly be developed.

This report presents a critical survey of existing information about several electrochemical and electronic detection techniques. The objective of this survey is to establish whether the practical sensitivity limits of these methods make it desirable for the Chemical Corps to seek intensively to find chemical means of applying these detection principles to reactions of the chemical agents, or whether these techniques offer no special potentialities that are superior to those of the more classical colorimetric methods.

For the present purposes, it will therefore be assumed that, if and when necessary, the chemical techniques needed to solve the specificity problem will be found. It will be assumed, then, that the potential (practical) sensitivity limits of the methods to be considered will be posed by factors (1) and (2) above, viz., the inherent signal-to-noise ratio, and the characteristics of available circuitry.

In the case of electrochemical techniques, the practical requirement that read-out must be on a rugged, portable deflecting element, such as an ammeter, voltmeter, or recorder, sets a limitation to the detection level that is higher than that which would be set by the inherent noise level. On the other hand, in the case of some of the electronic techniques, the practical detection limit is set by the signal-to-noise level of the detector itself, and not by the associated circuitry. (An electrochemical technique is one that operates in the solid or solution phase, through the medium of electrolytic conduction; an electronic technique is one that operates in the gas phase, through the medium of gaseous ions or free electrons).

In the special problem of the detection of atmospheric contaminants at very low concentrations, the question arises of whether to attempt to detect the component of interest at its pristine low concentration in a moderate or large volume of air, or to attempt to scrub it out of that volume into a small volume of a liquid prior to detection. That is, since the amount of substance, $\underline{x}$, is equal to its concentration, $\underline{c}$, times its volume, $\underline{v}$, is there a significant difference in detectability limits, for a given $\underline{x}$, when $\underline{c}$ is very small and $\underline{v}$ is moderate, compared to when $\underline{c}$ is moderate, and $\underline{v}$ is very small? This report considers that question with respect to the several specific techniques discussed.

II. THE FIELD OF ELECTROCHEMICAL DETECTION TECHNIQUES

A. The following analytical techniques are available for the detection of substances in solution:

1. Direct Weighing: The element of interest, or a compound related to it, is deposited at an electrode or stripped from an electrode by means of an electrochemical cell, and the gain or loss in weight of the electrode is determined with the use of an analytical balance.

2. Current Integration: The total amount of charge required to effect the electrochemical change is obtained by integration of the current-time curve, and if the electrode reaction is 100% efficient, the amount of the desired constituent follows from Faraday's law.

3. Titration: The principles involved are the same as in conventional titrimetry, except that the property utilized for detection of the end-point is an electrical one. Thus, the sensitivity of detection of a constituent depends upon the magnitude of the change in its conductivity, electrode potential, or diffusion current with changes in concentration.

4. Direct Electrical Measurement: Under favorable conditions a direct measurement of electrical conductivity, electrode potential, or diffusion current may be used in conjunction with the law relating that property to concentration to yield the latter quantity.

B. Present practice in the field of electroanalysis may be summarized as follows:

1. Electrodeposition

a) On solid electrodes: Metallic elements are usually deposited on the cathode in elementary form and the non-metals are deposited as compounds on the anode. The electrode material in most common use in this technique is platinum which may occasionally be plated with silver for the anodic deposition of the non-metals. The use of noble metal electrodes is particularly convenient in gravimetric analysis since their high chemical resistivity insures the maintenance of constant weight throughout the determination.

b) On the mercury pool electrode: This type of electrode has found wide use in qualitative and quantitative polarographic analysis. If is quite convenient for use in the controlled-potential separation of metals which are difficultly separable by chemical means. For example, the controlled potential mercury pool cathode makes possible the separation of large amounts of iron and nickel from their alloys, thus permitting the determination of even small amounts of aluminum, magnesium, and other elements which will remain in the electrolyte. In addition, the mercury pool electrode affords homogeneity of deposits and the high overvoltage of hydrogen eliminates the interference of hydrogen gas formation during deposition.

c) At controlled potentials: Many excellent separations of difficultly separable metals may be made through the use of controlled potential electrodeposition at a solid or liquid electrode. For example, this technique is used in brass analysis for the separation of lead and copper from each other and from iron and zinc. The electrodes usually used in controlled potential work are platinum gauze anodes and cathodes. The reference electrode used to measure the potential of the cathode is ordinarily the saturated calomel electrode. However, when the cathode is a mercury pool electrode, the silver-silver chloride reference electrode is used. The potential of the cathode is controlled either manually or automatically by varying the overall potential applied to the cell until the desired potential is read on a voltmeter connected across the cell electrodes.

d) By internal electrolysis: This is a form of electrodeposition which requires no external application of power to the cell to accomplish deposition. Electrolysis occurs spontaneously due to the difference in oxidation potential of two metals. For example, in the determination of small amounts of copper and bismuth in lead alloys, a pure lead anode and a platinum cathode are placed in a solution of the alloy, the electrodes are shorted, and copper and bismuth are deposited upon the platinum cathode while the lead anode slowly dissolves into solution.

Internal electrolysis may be considered as a form of controlled potential deposition since the cell potential may be controlled through the appropriate choice of anode material. A major disadvantage of this technique is that the relatively small driving voltage makes the cell resistance a critical factor in the rate of metal deposition. In addition, the smaller the difference in oxidation potentials of the metals, the longer is the time required for quantitative deposition. Therefore, internal electrolysis is not efficient for the separation of metals whose oxidation potentials lie close together. However the method is satisfactory for small quantities of metals and less critical separations.

2. Potentiometric Titration

a) Acid-base: The most frequently used indicator electrodes are the quinhydrone and the glass electrodes whose potentials vary directly with the pH of the electrolyte solution. The saturated calomel electrode is widely used in conjunction with the above as a reference electrode. End points in potentiometric acid-base titrations are determined graphically from a plot of potential or pH against the volume of titrant added or by titration to a previously calculated end point potential.

b) Precipitation: The titrations of greatest significance are those involving insoluble salts of silver or mercury. The anions commonly determined include Cl^-, Br^-, I^-, CN^-, CNS^-, $SO_4^=$, etc. The indicator electrode may be of silver or mercury or an electrode whose potential is determined by the anion in question such as a platinum wire electrode immersed in a solution of free iodine and iodide ions. Titration end points are determined either graphically from potential versus titrant volume plot or by titration to the previously calculated end point potential. However, the sharpness of the end point depends upon the completeness of the precipitation reaction in question (solubility product of the precipitate). The sharpest end points are therefore obtained where precipitation results in a salt having a very low solubility product such as AgI.

c) Oxidation - Reduction: Some frequently used oxidants in these titrations are Ce^{4+}, MnO_4^-, $Cr_2O_7^=$, IO_3^-, BrO_3^-, etc. Commonly used reductants are Fe^{++}, AsO_3^{---}, Ti^{+++}, Cr^{++}, etc. The indicator electrode used in these titrations must be resistant to attack by the solution so that it merely serves to transfer electrons from the solution to the external circuit. Therefore metals such as platinum, gold, and occasionally silver and mercury serve as good indicator electrodes. Methods of end pointlocation are the same as those used in acid-base and precipitation titrations. Results of high precision are readily obtained with this technique since redox end points are characterized by larger potential breaks at the end point than are experienced with the other types of potentiometric titration.

3) Conductimetric Titration

a) Acid-Base: The apparatus used is the customary glass conductance cell fitted with a pair of platinum electrodes and the Wheatstone bridge type of electrical circuit arrangement. The principal advantage of the conductimetric technique over other methods is that it allows the use of titration reactions which are too incomplete for end point detection by the other methods. This is possible because end point location in conductimetric titration is made graphically as the point of intersection of two straight lines obtained from measurements of conductance made before and after the actual end point. Weak acids such as phenol, hydroquinone, and boric acid are therefore readily titrated conductimetrically. Another advantage is that conductimetry is applicable to very dilute solutions with little loss in precision and accuracy.

b) Precipitation: The apparatus used is the same as that previously described. In order to obtain a V-shaped curve from the plot of conductance versus titrant volume for accurate end point location, it is essential that the ionic conductance of the cation to be determined should be much greater than the ionic conductance of the cationic portion of the precipitant. This follows from the fact that the overall result of precipitation is the replacement of the cation to be determined with the cation of the precipitant.

4. Coulometry

a) Electrodeposition: This analytical technique is based upon Faraday's principle that the quantity of material undergoing electrode reaction is directly proportional to the quantity of electricity applied. Therefore the amount of an element present in solution may be determined by measuring the total quantity of electricity required to effect its complete deposition. However, it is a basic requirement that the electrodeposition reaction must proceed with 100% current efficiency.

The greatest versatility of the method is achieved by carrying out deposition at a controlled potential mercury pool cathode since it enables the determination of a particular cation when others are present in the same solution. A mercury cathode also allows the experimental determination of optimum deposition potentials where data is not available. This electrode also functions over a wider potential range without interference from hydrogen gas evolution and enhances the establishment of conditions for 100% current efficiency.

The standard instrument used to measure the number of coulombs of electricity passed in deposition is the hydrogen-oxygen coulometer. Accuracy of 0.1% is obtained down to about the ten coulomb level. For measurements in the range of 1-10 coulombs, a titration coulometer is used which gives an accuracy of 1.0%. This instrument consists of a platinum cathode and a silver anode immersed in an electrolyte mixture of KBr and K_2SO_4. The number of coulombs passed are determined by titrating with 0.1N HCl the OH^- ions produced in the net reaction:

$$Ag + Br^- + H_2O = AgBr + 1/2\ H_2 + OH^-$$

Coulomb measurement may also be accomplished by integration of the current-time curve for the particular cell reaction. Mechanical integrators for this purpose are commercially available from the Weston and Leeds and Northrup companies and have an accuracy of about ± 0.7%.

b) Electrosolution: This technique is the reverse of electrodeposition. It involves the measurement of the number of coulombs required to dissolve completely a given amount of an element from the surface of an anode. Both coulometers and mechanical integrators as previously discussed are used to measure the total applied charge in the cell reaction. Electrosolution is widely used commercially to determine the thickness of plating on metal surfaces.

c) Coulometric Titration: The method employs electrolytic generation of titrant which reacts stoichiometrically with the element to be determined. Through the use of a constant current source for titrant generation, the number of coulombs required may be calculated from the time taken to reach the end point. The basic requirements of coulometric titration are that the titrant-generating electrode reaction proceed with 100% current efficiency and that the generated titrant react stoichiometrically with the substance being determined. The titrant may be generated either internally or externally. Electrolytic generation of the titrant eliminates the need for standard solutions and makes possible the delivery of micro increments of titrant (10^{-10} M) not attainable even with micro-burets.

End points in coulometric titration are located by means of a plot of indicator electrode current versus titrant generation time using a polarized platinum wire electrode or by titration to a previously calculated end point potential.

5. Amperometry

This field of electroanalysis utilizes the principle that the diffusion current of a substance at a controlled potential dropping mercury electrode is directly proportional to its concentration in solution. Titration is therefore possible by the appropriate choice of titrant involving a precipitation or redox reaction. End points are obtained graphically from a plot of indicator electrode current versus titrant volume added.

III. ANALYSIS OF TRACE AMOUNTS

A. Macro versus micro approach:

Work in the field of the electroanalysis of traces may be roughly divided into two categories: (1) analysis of samples in macro volumes and low concentration, (2) analysis of samples in micro or semi-micro volumes and moderate concentration. For example, the determination of one gamma of silver in a 100 ml. volume represents a 10^{-7} M concentration of silver whereas the same amount of silver in a one ml. volume represents a concentration of 10^{-5} M.

The literature in the field indicates that the bulk of the determinations reported deal with trace amounts in macro volume and low concentration. Techniques for analysis of traces in micro volume have not as yet been sufficiently developed to yield results comparable to those obtained in macro volume.

B. Limitations to Trace Analysis:

1. Contamination

This is a serious problem when dealing with micro amounts of sample. The source of contamination with either the same or an interfering element may be in the reagents used or foreign particles on the walls of the glass equipment which the solution contacts. The measures taken to combat such contamination are the scrupulous cleaning of all glass equipment and the electrolysis of reagents before use.

2. Adsorption

Since glass surfaces readily tend to adsorb trace elements from solution, a serious source of error in micro work is thus presented by this phenomenon. This adsorption process may also be irreversible enough to compete with the electrodeposition process, this causing incomplete deposition. Adsorption errors may be minimized by coating the exposed glass surfaces of apparatus with a wax preparation or by depositing the element of interest from a solution of a stable complex.

3. Colloidal Phenomena

Investigators have met with considerable difficulty in attempting the electroanalysis of trace amounts of radioactive elements due to their tendency toward radiocolloid formation. The phenomenon consists of the precipitation of radioactive elements from solution as colloidal particles although the solubility product has not been exceeded. A frequently postulated structure for radio-colloids is that of an inactive colloidal base such as silica or dust upon which radio-active atoms have been adsorbed. Intensive study of the phenomena has lead to the recognition of five factors influencing radio-colloid formation.

a) Solubility: The tendency of radio-active elements to form insoluble compounds with a component of the solution favors radio-colloid formation. The addition of a complexing agent can alleviate this difficulty.

b) Foreign Particules: Minute suspended particules act as nuclei for radio-colloid formation through surface adsorption. Complete removal of all suspended matter is therefore essential.

c) Solvent: It has been shown experimentally that particular solvents encourage radio-colloid formation with certain radio-active elements. For example, lead and bismuth do not form radio-colloids in dioxane or acetone but do in methanol, ethanol, and water. Therefore careful solvent selection is important.

d) Electrolytes: There is experimental evidence to show that the addition of small concentrations of foreign electrolytes such as HCl, HNO_3, and H_2SO_4 to solutions of radio-active elements tends to suppress radio-colloid formation. This may be due to possible complexing action of the electrolyte or alteration of the charge distribution in the solution.

e) Time: Investigators have found that the amount of radiocolloid formation increases with increasing age of the solution. Obviously it is important to work with freshly prepared solutions of radio-active material to minimize this source of error.

4. Solubility

This represents a serious limitation in the electroanalysis of traces by deposition of a compound at an electrode. In extremely dilute solutions, the solubility of the compound may make deposition impossible. The solubility difficulty is also encountered in trying to wash an electrode bearing a micro deposit before weighing in a gravimetric determination.

5. Sensitivity of Measuring Instruments

a) Balance: Since electrodeposition analysis is essentially gravimetric in nature, the sensitivity of the analytical micro balance is an important limitation is this technique. Commercially available micro balances have a sensitivity of about one gamma. Balances with almost this order of sensitivity might conceivably be designed for use under field conditions.

b) Electrical Meters: The techniques of amperometry, potentiometry, and coulometry are all based upon the measurement of small amounts or changes in current, voltage, or resitance. Therefore, the limits of sensitivity of these methods correspond to the limits of reliability of the ammeters, voltmeters, and ohmeters which are employed as the measuring instruments. The reliabilities of modern commercially available, inexpensive, and rugged electrical equipment may be taken to approximately:

Ammeters - 0.01 microamps
Voltmeters - 1.0 millivolts
Ohmeters - 0.1 ohms

6. Physical Laws Governing Property Measured

a) Limitation imposed by the Nernst equation: It can be readily shown with the aid of a few simple calculations employing the Nernst equation that a potentiometric titration may be performed successfully only when the oxidation potentials of the titrant and sample are sufficiently far apart to ensure complete reaction by the time the equivalence point potential is reached. As an illustration, we may consider the potentiometric titration of ferrous ion with ceric ion in the reaction:

$$Ce^{4+} + Fe^{2+} = Ce^{3+} + Fe^{3+}$$

The variation in potential for both the ferrous-ferric and the cerous-ceric systems during titration is given by the Nernst equation (1):

$$E = E^{o} + 0.059 \log \frac{(oxid)}{(red)}$$

As the titration proceeds, the potential of the ferric-ferrous system increases while that of the ceric-cerous system decreases in accordance with the Nernst equation. At the equivalence point, the potential of both systems are equal. If the proper titrant has been chosen, the attainment of the end point potential also marks the quantitative conversion of ferrous ion to ferric ion. That this is true may be shown by calculating the equilibrium constant "K" for the reaction from the relationship (2):

$$(E^{o}_{Ce} - E^{o}_{Fe}) = 0.059 \log K$$

The calculated value of $K = 10^{12}$ confirms the quantitative conversion of ferrous ion to ferric ion.

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(1) I.M. Kolthoff & E.B. Sandell, "Textbook of Quantitative Inorganic Analysis", Macmillan Co., 3rd Ed. 1952 p. 157
(2) Ibid., p. 467

b) Breakdown of the Nernst equation at very low concentration: Rogers (3) has reported that the experimentally determined potential of a cationic electrode of the type : $M^{+} + e = M$ varied considerably from the value calculated from the Nernst equation when (M^{+}) was of the order of 10^{-7} M. He attributed this discrepancy to the practice of assigning a value of unity to the activity of M (pure metal) in the Nernst equation calculation. Rogers postulated that the activity of the pure metal (M) is less than unity since deposition at extremely low concentrations of M^{+} on a platinum electrode results in a discontinuous layer of metal of less than monomolecular thickness. Hence the simplified Nernst equation does not adequately describe the potential of a cationic electrode at extremely low concentrations. A more complex equation must be used which allows for the deviation from unity of the activity of the pure metal (M).

IV Amperometric Titration of Traces

A. Theoretical Considerations

In the main, two types of indicator electrodes have been used in amperometric titration. They are the dropping mercury electrode and the rotating platinum electrode. To complete the cell circuit, either a saturated calomel or a silver-silver chloride reference electrode is coupled with either of the above. A potentiometer impresses a constant potential across the cell electrodes during titration while a galvanometer with a sensitivity of 0.01 micro-amps tracks the changes in diffusion current of the sample.

The end point of the titration may be determined graphically as the point of intersection of two straight lines representing the changes in diffusion current of the sample and titrant. The graph therefore is a plot of diffusion current (micro-amp) as ordinate and volume of titrant (ml) is abscissa. Since amperometry is actually an application of the polarographic analysis technique, the basic theoretical principles are the same. In this discussion, we shall make use of the Ilkovic equation which expresses the relationship between the diffusion current of a cation or anion and its concentration (4):

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(3) L. B. Rogers, Anal. Chem., 22, 1386 (1950)

$$i_d = 607\ n\ D^{1/2}\ C\ m^{2/3}\ t^{46}$$

where i_d = diffusion current (micro-amps)

n = number of electrons involved in electrode reaction

D = diffusion coefficient (cm^2/sec)

C = concentration of cation or anion (millimoles/liter)

m = mass of mercury drop from dropping mercury electrode (mg/sec.)

t = drop time (sec)

From the foregoing equation it is possible to calculate the maximum practical sensitivity of both micro and macro titrations under an arbitrary set of assumed conditions. For example, to calculate the maximum sensitivity of a micro titration we may assume the following field conditions:

a) The initial volume of solution is 1.0 ml.

b) The titrant is delivered in increments of 1 lambda (10-3ml), since this is the smallest amount deliverable with 1% accuracy.

c) The smallest total increase in diffusion current that can serve to define a straight line with an accuracy of 1-5% is 0.10 micro-amp.

d) The equivalence point is reached after the addition of 2 lambda of titrant.

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(4) I. M. Kolthoff & J. J. Lingane, "Polarography", Interscience Publishers, N. Y., 1952 Vol. 1, p. 63

e) The addition of 2 lambda of titrant beyond the equivalence point results in an increase of 0.10 micro-amp of diffusion current.

Fig. 1 shows a typical graphical plot of a micro titration carried out under the above arbitrary conditions. To illustrate a typical calculation of this maximum sensitivity, we will assume our titrant to be lead nitrate and take $m^{2/3}\ t^{1/6} = 2.28$. By substitution in the diffusion current equation, we calculate that a concentration 1.1×10^{-5} M lead ion is required for an increase of 0.10 micro-amp. in diffusion current. Since it is desired that the addition of 2 lambda of titrant to 1.0 ml. of solution shall result in a final lead ion concentration of 1.1×10^{-5} M, the original concentration of our titrant must have been 5.5×10^{-3} M. Also since 2 lambda of 5.5×10^{-3} M titrant is equivalent to 1.0 ml. of our unknown solution, the conentration of our unknown must be 1.1×10^{-5} M. Thus the calculation shows that the practical limit of detection and analysis in a 1 ml. volume is a concentration of 10^{-5} M.

Similarly, the theoretical maximum sensitivity for a macro titration may be calculated by fixing the following conditions:

a) The initial volume of solution is taken as 100.0 ml.

b) The titrant is delivered in increments of 0.10 ml.

c) The smallest total increase in diffusion current that may serve to define a straight line with 1-5% accuracy is 0.10 micro-amp.

d) The equivalence point is reached after the addition of 0.10 ml. of titrant.

e) The addition of 100.00 ml. of titrant beyond the equivalence point results in an increase of 0.10 micro-amps of diffusion current.

Fig. 2 shows a typical graphical plot of a macro titration carried out under the above assumed conditions. Again assuming our titrant to be lead nitrate and that $n^{2/3} t^{1/6} = 2.28$, we may illustrate the calculation of maximum sensitivity for the macro titration. Appropriate substitution in the diffusion current equation shows that a concentration of 1.1×10^{-5} M of lead ion is required for an increase of 0.10 micro-amp in diffusion current. Since the addition of 100 ml. of titrant to 100 ml. of solution yielded a final lead ion concentration of 1.1×10^{-5} M, the original concentration of our titrant must have been 2.2×10^{-5} M. Furthermore, since 0.10 ml. of the 2.2×10^{-5} M titrant is equivalent to 100 ml. of our unknown solution, the concentration of our unknown must be 2.2×10^{-8} M.

Table I lists the calculated maximum sensitivities for various titrants under both micro and macro conditions and subject to the conditions outlined above, with $m^{2/3} t^{1/6} = 2.28$.

TABLE I

Titrant:	Diffusion Coefficient (5) (cm²/sec)	Calculated Maximum Sensitivity (Moles/Liter)
MICRO TITRATION:		
H^+	9.3×10^{-5}	8.0×10^{-6}
Li^+	1.0×10^{-5}	2.2×10^{-5}
Pb^{++}	9.8×10^{-6}	1.1×10^{-5}
Cu^{++}	7.2×10^{-6}	1.3×10^{-5}
OH^-	5.2×10^{-5}	1.0×10^{-5}
SO^{--}	1.1×10^{-5}	1.1×10^{-5}
$Fe(CN)_6^{---}$	8.9×10^{-6}	2.4×10^{-5}
MACRO TITRATION:		
H^+	9.3×10^{-5}	1.5×10^{-8}
Li^+	1.0×10^{-5}	4.6×10^{-8}
Pb^{++}	9.8×10^{-6}	2.2×10^{-8}
Cu^{++}	7.2×10^{-6}	2.7×10^{-8}
OH^-	5.2×10^{-5}	2.0×10^{-8}
SO_4^{--}	1.1×10^{-5}	2.2×10^{-8}
$Fe(CN)_6^{---}$	8.9×10^{-6}	4.9×10^{-8}

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(5) I. M. Kolthoff and J. J. Lingane, *Ibid*, p. 52

B. Comparison with Experimental Results:

In the following discussion of reports in the literature concerning micro and macro amperometric determinations, all calculations regarding maximum sensitivity are based upon data given in the reports and upon the condition that 0.10 microamps is the minimum increase in diffusion current necessary to define a straight line in a graphical plot.

The amperometric determination of fluorine has been investigated by Langer (6). The titrant was 2.5×10^{-3}M to 2.5×10^{-4}M thorium nitrate and the initial solution volumes were 50 ml. (Macro) and 5 ml. (semi-micro). A dropping mercury electrode with a drop time of 3.2 sec. was the indicator electrode. The addition of 0.10 ml. of excess titrant resulted in an increase of 0.02 microamps in diffusion current. The minimum concentration of fluorine reported was 2.0×10^{-5}M, determined with an accuracy of 4.6%. The calculated minimum florine concentration detectable in the macro titration is 5.0×10^{-5}M using 2.5×10^{-3}M titrant while in the semi-micro titration the same concentration limit obtains with the 2.5×10^{-4}M titrant.

Langer (7) has also reported the amperometric titration of copper in an initial solution volume of 45 ml. with 0.01 M benzoinoxime as titrant and a mercury indicator electrode with a drop time of 3.0 sec. An excess of 0.10 ml. of titrant caused a 0.10 microamp increase in diffusion current. The minimum concentration of copper reported was 2.0×10^{-4} M, determined with an accuracy of 1.0%. The calculated minimum concentration of copper detectable is 4.0×10^{-5} M.

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(6) A. Langer, Ind. & Eng. Chem., Anal. Ed., 12, 511 (1940)
(7) Idem, Ibid, 14, 283 (1942)

Kolthoff and Cohn (8) determined phosphate amperometrically in an initial solution volume of 50 ml. with 0.10 M uranyl acetate as the titrant. The diffusion current increased by 0.70 microamps with the addition of 0.10 ml. of excess titrant. The minimum concentration of phosphate reported was 10^{-4} M, determined with an accuracy of 4.0%. The calculated minimum concentration of phosphate detectable is 6.0×10^{-5}M.

Kolthoff and Harris (9) developed the amperometric analysis of mercaptan sulfur using a rotating platinum indicator electrode, an initial solution volume of 100 ml. and 5×10^{-3} M silver nitrate as the titrant. A titrant excess of 0.10 ml. produced a diffusion current increase of 0.70 microamps. The minimum concentration of mercaptan sulfur reported was 6.3×10^{-5} M, determined with an accuracy of 2.0%. The calculated minimum concentration limit is 1.5×10^{-6} M.

The amperometric determination of chromate was accomplished by Kolthoff and May (10) using a rotating platinum indicator electrode, and initial solution volume of 50 ml. and 0.01 M ferrous ammonium sulfate as the titrant. The diffusion current increased by 1.30 microamps with the addition of 0.10 ml. of excess titrant. The minimum concentration of chromate reported was 10^{-4} M, determined with an accuracy of 0.50%. The calculated minimum chromate limit is 4.0×10^{-6} M.

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(8) I. M. Kolthoff & G. Cohn, Ind. & Eng. Chem., Anal. Ed., 14, 412 (1942)
(9) I. M. Kolthoff & W. E. Harris, Ibid, 18, 161 (1946)
(10) I. M. Kolthoff & D. R. May, Ibid, 18, 208 (1946)

Laitinen, Jennings, and Parks (11) described the amperometric determination of chloride, bromide, and iodide using a rotating platinum indicator electrode, an initial solution volume of 100 ml., and 0.10 M silver nitrate as the titrant. The addition of 0.10 ml. of excess titrant resulted in an increase in diffusion current of 7.0 microamps. The minimum concentration of each halide reported was 10^{-4} M, determined with an accuracy of 2.0%. The calculated minimum limit for each halide is 3.0×10^{-6} M.

A method for amperometric cyanide analysis has been developed by Laitinen, Jennings, and Parks (12) employing 2×10^{-4} M silver nitrate as the titrant, an initial solution volume of 100 ml., and a rotating platinum indicator electrode. No information, however, was given regarding the increase in diffusion current with the addition of excess titrant. The minimum concentration of cyanide reported was 4×10^{-6} M, determined with an accuracy of 4.9%.

Kolthoff and Bovey (13) described the amperometric titration of styrene using a rotating platinum electrode, an initial solution volume of 100 ml., and 1.78×10^{-3} M potassium bromide-bromate solution as the titrant. The addition of 0.10 ml. of excess titrant resulted in an increase of 2.0 microamps in diffusion current. The minimum concentration of styrene reported was 5.8×10^{-5} M, determined with an accuracy of 1.9%. The calculated minimum limit is 1.8×10^{-7} M.

Kolthoff and Gregor (14) developed the amperometric titration of barium with a mercury indicator electrode of 3.6 sec. drop time, an initial solution volume of 50 ml., and 0.01 M potassium chromate as the titrant. An increase of 0.20 microamps in diffusion current was noted with the addition of 0.10 ml. of excess titrant. The minimum concentration of barium reported was 10^{-3} M, determined with an accuracy of 3.0%. The calculated minimum limit is 2.0×10^{-5} M.

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(11) H. A. Laitinen, W. P. Jennings, & T. O. Parks, Ind. & Eng. Chem., Anal. Ed., 18, 355, (1946)
(12) Idem, Ibid, 18, 574 (1946)
(13) I. M. Kolthoff & F. A. Bovey, Ibid, 19, 498 (1947)
(14) I. M. Kolthoff & H. P. Gregor, Anal. Chem., 20, 541 (1948)

The amperometric analysis of diamidine salts was accomplished by Conn (15) using a dropping mercury indicator electrode, an initial solution volume of 5 ml., and 0.0775 M sodium alizarinsulfonate as the titrant. A diffusion current increase of 3.0 microamps was noted upon the addition of 0.10 ml. of excess titrant. The minimum concentration of phenamidine reported was 3.1×10^{-3} M, determined with an accuracy of 0.50%. The calculated minimum limit is 9.6×10^{-5} M.

Gale and Mosher (16) have reported the amperometric titration of vanadium employing a pair of polarized platinum electrodes, an initial solution volume of 20 ml., and 0.025 M ferrous ammonium sulfate as the titrant. The addition of 0.10 ml. of excess titrant resulted in a diffusion current increase of 14.0 microamps. The minimum concentration of vanadium reported was 2.4×10^{-4} M, determined with an accuracy of 2.0%. The calculated minimum limit is 2.5×10^{-6} M.

Parks and Agazzi (17) reported the amperometric analysis of vanadium and chromium using a rotating platium indicator electrode, an initial solution volume of 30 ml., and 10^{-3} M ferrous ammonium sulfate as the titrant. No data were given concerning the increase in diffusion current with addition of excess titrant. The minimum concentrations of vanadium and chromium reported were 3.0×10^{-6} M, determined with an accuracy of about 30%.

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(15) J. B. Conn, Ibid, 20, 585 (1948)
(16) R. W. Gale & E. Mosher, Anal. Chem., 22, 942 (1950)
(17) T. D. Parks & E. J. Agazzi, Ibid, 22, 1179 (1950)

Lead has been determined amperometrically by Kolthoff and Pan (18) using 5.0×10^{-3} M potassium dichromate as the titrant, an initial solution volume of 50 ml., and a mercury indicator electrode with drop time of 3.0 sec. The addition of 0.10 ml. of excess titrant resulted in a diffusion current increase of 2.8 microamps. The minimum concentration of lead reported was 10^{-3} M, determined with an accuracy of 0.30%. The calculated limit is 6.0×10^{-7} M.

Kolthoff and Langer (19) developed the amperometric titration of nickel using an initial solution volume of 50 ml., a mercury indicator electrode with drop time of 2.8 sec., and 0.01 M dimethylglyoxime as the titrant. The diffusion current increase was 0.20 microamps upon the addition of 0.10 ml. of excess titrant. The minimum concentration of nickel reported was 10^{-4} M, determined with an accuracy of 2.0%. The calculated minimum concentration is 2.0×10^{-5} M.

Kolthoff and Langer (20) reported the amperometric determination of cobalt using a mercury indicator electrode with a drop time of 3.0 sec., an initial solution volume of 50 ml., and 0.10 M alpha-nitroso beta-naphthol as the titrant. The addition of 0.10 ml. of excess titrant caused a 1.0 microamp increase in diffusion current. The minimum concentration of cobalt reported 5.0×10^{-4} M, determined with an accuracy of 1.0%. The calculated minimum limit is 4.0×10^{-5} M.

Sulfate has been amperometrically determined by Kolthoff and Pan (21) with an initial solution volume of 50 ml., a mercury indicator electrode with a drop time of 3.0 sec., and 0.01 M lead nitrate as the titrant. A diffusion current increase of 0.12 microamps was noted upon the addition of 0.10 ml. of excess titrant. The minimum concentration of sulfate reported was 10^{-3} M, determined with an accuracy of 0.5%. The calculated minimum limit is 4.0×10^{-5} M.

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(18) I. M. Kolthoff & Y. D. Pan, J. Am. Chem. Soc., 61, 3402 (1939)
(19) I. M. Kolthoff & A. Langer, J. Am. Chem. Soc., 62, 211 (1940)
(20) Idem, Ibid, 62, 3172 (1940)
(21) I. M. Kolthoff & Y. D. Pan, Ibid, 62, 3332 (1940)

Kolthoff and Pan (22) devised an amperometric titration of oxalate employing an initial solution volume of 50 ml., a mercury indicator electrode, and 0.01 M lead nitrate as the titrant. No data was given regarding increase in diffusion current with addition of excess titrant. The minimum concentration of oxalate reported was 10^{-3} M, determined with an accuracy of 0.5%.

An amperometric determination of lead was described by Kolthoff and Pan (23) using initial volume of 50 ml., 0.01 M sodium oxalate as the titrant, and a mercury indicator electrode. No data were given regarding the increase in diffusion current with addition of excess titrant. The minimum concentration of lead reported was 10^{-3} M, determined with an accuracy of 0.5%.

Smith, Kolthoff, and Spillane (24) have reported the amperometric analysis of Vitamin E using a mercury indicator electrode with a drop time of 3.72 sec., an initial solution volume of 90 ml., and 9.79×10^{-3} M gold chloride as the titrant. The addition of 0.10 ml. of excess titrant resulted in a diffusion current increase of 0.10 microamps. The minimum concentration of Vitamin E reported was 3.0×10^{-4} M, determined with an accuracy of 0.3%. The calculated minimum limit is 2.0×10^{-5} M.

Laitinen and Kolthoff (25) determined arsenic amperometrically employing a rotating platinum indicator electrode, an initial solution volume of 100 ml., and 1.7×10^{-3} M potassium bromate as the titrant. A diffusion current increase of 0.80 microamps resulted from the addition of 0.10 ml. of excess titrant. The minimum concentration of arsenic reported was 3.0 x 10^{-5} M, determined with an accuracy of 0.3%. The calculated minimum limit is 3.4 x 10^{-7} M.

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(22) I. M. Kolthoff & Y. D. Pan, J. Amer. Chem. Soc., 62, 3335 (1940)
(23) Idem, Ibid, 62, 3336 (1940)
(24) L. I. Smith, I. M. Kolthoff, & L. J. Spillane, Ibid, 64, 646 (1942)
(25) H. A. Laitinen & I. M. Kolthoff, J. Phys. Chem., 45, 1089 (1941)

The amperometric titration of silver was reported by Laitinen and Kolthoff (26) using a rotating platinum indicator electrode, an initial solution volume of 100 ml., and 1.11 x 10^{-2} M potassium chloride as the titrant. The addition of 0.10 ml. of excess titrant caused a 0.70 microamp increase in diffusion current. The minimum concentration of silver reported was 10^{-3} M, determined with an accuracy of 0.5%. The calculated minimum limit is 6.6 x 10^{-6} M.

Hirozawa and Brasted (27) carried out the amperometric analysis of sulfamates using a mercury indicator electrode, an initial solution volume of 30 ml., and 0.10 M sodium nitrite as the titrant. The addition of 0.10 ml. of excess titrant resulted in diffusion current increase of 4.0 microamps. The minimum concentration of sulfamic acid reported as 4.0 x 10^{-4} M, determined with an accuracy of 4.0%. The calculated minimum limit is 2.0 x 10^{-5} M.

C. Conclusion:

Thus, it may be seen from the above comparison of experimental results and calculations of maximum sensitivity that present techniques in the field of amperometric titrations represent in general the limit to which this approach may reasonably be pushed with current instrumentation. This limit is roughly 10^{-5} M for 1 ml. samples and 10^{-8} M for 100 ml.

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(26) Idem, Ibid, 45, 1089 (1941)
(27) S. T. Hirozawa & R. C. Brasted, Anal. Chem., 25, 221 (1953)

samples. If solutions more dilute than these limits are to be analyzed, a different electro-analytical approach should be sought.

A summary of the work done in the field of amperometry as previously discussed is given in Table II.

TABLE II

Material	Minimum Conc. Reported (Moles/ Liter)	Per Cent Accuracy	Minimum Conc. Calculated (Moles / Liter)	Reference
Arsenic	3.0×10^{-5}	0.30	3.4×10^{-7}	(25)
Barium	1.0×10^{-3}	3.0	2.0×10^{-5}	(14)
Chromium	3.0×10^{-6}	30.0	No Data	(17)
Cobalt	5.0×10^{-4}	1.0	4.0×10^{-5}	(20)
Copper	2.0×10^{-4}	1.0	4.0×10^{-5}	(7)
Fluorine	2.0×10^{-5}	4.6	5.0×10^{-5}	(6)
Lead	1.0×10^{-3}	0.30	6.0×10^{-7}	(18)
Nickel	1.0×10^{-4}	2.0	2.0×10^{-5}	(19)
Silver	1.0×10^{-3}	0.50	6.6×10^{-6}	(26)
Sulfur	6.3×10^{-5}	2.0	1.5×10^{-6}	(9)
Vanadium	3.0×10^{-6}	30.0	No Data	(17)
Bromide	1.0×10^{-4}	2.0	3.0×10^{-6}	(11)
Chloride	1.0×10^{-4}	2.0	3.0×10^{-6}	(11)
Cyanide	4.0×10^{-6}	4.9	No Date	(12)
Oxalate	1.0×10^{-3}	0.50	No Data	(22)
Iodide	1.0×10^{-4}	2.0	3.0×10^{-6}	(11)
Phospate	1.0×10^{-4}	4.0	6.0×10^{-5}	(8)
Phenamidine	3.1×10^{-3}	0.50	9.6×10^{-5}	(15)
Styrene	5.8×10^{-5}	1.9	1.8×10^{-7}	(13)
Sulfamic Acid	4.0×10^{-4}	4.0	2.0×10^{-5}	(27)
Vitamine E	3.0×10^{-4}	0.30	2.0×10^{-5}	(24)

V. Coulometric Analysis of Traces

A. Theoretical Considerations:

End points in electro-deposition and electro-solution analysis are obtained as the intersection of the straight line plot of cell current decay versus generation time with the residual current base line. Coulometric titration end points are determined amperometrically with a plot of diffusion current change of titrant and sample versus generation time.

The coulometric technique is based upon Faraday's law relating the amount of material undergoing reaction at an electrode to the total quantity of electricity passed through the cell. The theoretical maximum sensitivity of a coulometric titration may be readily calculated by employing Faraday's law and the following arbitrary conditions:

a) The minimum constant generation current used in titration is 50 microamps.

b) Background current of approximately 1.0 microamp is considered negligible.

c) The minimum elapsed titration time measurable with an accuracy of 1% is 10.0 sec. since the reproducibility of the mechanical response of the current generator to the cut-off switch is about 0.10 sec.

To illustrate the calculation of the theoretical maximum sensitivity under the above arbitrary conditions, we first apply the Faraday relationship that approximately 10^5 coulombs are required for the reaction of one equivalent weight of material at an electrode. Since we have assumed the generation current to be 50 micro-amps and the titration time to be 10.0 seconds, the passage of 5.0×10^{-4} coulombs occurs during the titration. It then follows from Faraday's law that the maximum theoretical sensitivity of the titration is 5.0×10^{-9} equivalents of sample.

The theoretical maximum sensitivity in a coulometric electro-deposition or solution may similarly be estimated on the basis of the assumption of a constant generation current of 1.0 micro-amps* flowing for a time interval of 10 seconds. This would correspond to a total chemical equivalence of 10^{-10} equivalents.

B. Comparison with Experimental Results:

The literature shows that coulometric titration has found wider application than electro-deposition and electro-solution analysis where the problems of current efficiency and overvoltage must be overcome.

In the following discussion of reports on coulometric analysis, the calculated maximum sensitivity in each case is taken as 5.0×10^{-9} equivalents as derived from the previously stated set of arbitrary conditions.

Sease, Niemann, and Swift (28) have reported the coulometric titration of thiodiglycol using platinum indicator electrodes, an initial solution volume of 10.0 ml., and electrolytically generated bromine with a current value of 2.0 milliamps (2.0×10^{-8} equiv./sec). The minimum amount of thiodiglycol reported was 6.4×10^{-7} equiv. determined with an accuracy of 2.0%. The calculated minimum amount of thiodiglycol is 5.0×10^{-9} equiv.

Farrington and Swift (29) described the coulometric analysis of arsenic using platinum indicator electrodes, an initial solution volume of 45 ml., and electrolytically generated chlorine as the titrant with a current rate of 1.0 milliamp (1.0×10^{-8} equiv./sec.). The minimum amount of arsenic reported was 8.0×10^{-7} equiv., determined with an accuracy of 0.60%.

The coulometric titration of cerium and chromium has been accomplished by Cooke and Furman (30) using a solution volume of 35 ml., platinum indicator electrodes, and electrolytically generated ferrous ion as the titrant with a current rate of 5.0 milliamps. The minimum amount of cerium reported was 1.0 x 10^{-5} equiv., determined with an accuracy of 1.0%.

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(28) J. W. Sease, C. Niemann, & E. H. Swift, Ind. & Eng. Chem., Anal. Ed., 19, 197 (1947)

(29) P. S. Farrington & E. H. Swift, Anal. Chem., 22, 889 (1950)

(30) W. D. Cooke & N. H. Furman, Ibid, 22, 896 (1950)

Carson (31) developed the coulometric analysis of 8-quinolinol using platinum indicator electrodes, a solution volume of 50 ml., and electrolytically generated bromine titrant at a current rate of 10.0 milliamps (1.0 x 10^{-7} equiv./sec.). The minimum amount of 8-quinolinol reported was 1.1 x 10^{-5} equiv., determined with an accuracy of 0.50%.

Arthur and Donahue (32) developed the coulometric titration of iron employing a solution volume of 105 ml., electrolytically generated titanous ion titrant at a current rate of 50.0 milliamps (5.0 x 10^{-7} eqiv./ sec.), and platinum indicator electrodes. The minimum amount of iron reported was 1.0 x 10^{-3} equiv., determined with an accuracy of 0.20%.

Uranium was determined coulometrically by Furman, Bricker, and Dilts (33) using electrolytically generated ceric ion titrant at a current rate of 30 microamps (3.0 x 10^{-10} equiv./sec.), an initial solution volume of 25 ml., and platinum-iridium foil indicator electrodes. The minimum amount of uranium reported was 4.2 x 10^{-8} equiv., determined with an accuracy of 8.0%.

Maganese has been coulometrically titrated by Cooke, Reilly, and Furman (34) using platinum-iridium foil indicator electrodes, a solution volume of 5.0 ml., and electrolytically generated ferrous ion titrant at a current rate of 5.0 microamps (5.0 x 10^{-11} equiv./sec.). The minimum amount of manganese reported was 2.7 x 10^{-10} equiv., determined with an accuracy of 5.0%.

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(31) W. N. Carson Jr., Ibid, 22, 1565 (1950)
(32) P. Arthur & J. F. Donahue, Anal. Chem., 24, 1612 (1952)
(33) N. H. Furman, C. E. Bricker, & R. V. Dilts, Ibid, 25, 482 (1953)
(34) W. D. Cooke, C. N. Reilly, & N. H. Furman, Ibid, 24, 205 (1952)

Lord Jr., O'Neill, and Rogers (35) determined silver by alternate electro-deposition and electro-solution at a platinum electrode. Since the current used was variable, the total number of coulombs required for electro-solution of the silver was determined by integration of the area under the current-time curve for the cell. The initial solution volume was 0.02 to 25 ml. The minimum amount of silver reported was 4.6×10^{-12} equiv., determined with an accuracy of 20.0%.

Myers and Swift (36) reported the coulometric titration of arsenic using platinum indicator electrodes, an initial solution volume of 50 ml., and electrolytically generated bromine titrant at a current rate of 1.0 milliamps (1.0×10^{-8} equiv./sec.). The minimum quantity of arsenic reported was 9.2×10^{-7} equiv., determined with an accuracy of 1.2%.

Meier, Myers and Swift (37) developed the coulometric analysis of chromium and vanadium using a solution volume of 45 ml., platinum indicator electrodes, and electrolytically generated cuprous ion titrant at a current rate of 10.0 milliamps (1.0×10^{-7} equiv./sec.). The minimum quantity of chromium reported was 1.0×10^{-6} equiv., determined with an accuracy of 1.0%. The minimum amount of vanadium reported was 7.0×10^{-7} equiv., determined with an accuracy of 0.20%.

The coulometric analysis of iron was described by Furman and Cooke (38) using a solution volume of 25 ml., platinum indicator electrodes, and electrolytically generated ceric ion titrant at a current rate of 25.0 milliamps (2.5×10^{-7} equiv./sec.). The minimum quantity of iron reported was 9.8×10^{-5} equiv., determined with an accuracy of 0.10%.

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(35) S. S. Lord Jr., R. C. O'Neill, & L. B. Rogers, Anal. Chem. 24, 209 (1952)
(36) R. J. Myers & E. H. Swift, J. Amer. Chem. Soc., 70, 1047 (1948)
(37) D. J. Meier, R. J. Myers, & E. H. Swift, Ibid, 71, 2340 (1949)
(38) N. H. Furman & W. D. Cooke, Anal. Chem., 23, 945 (1951)

Cooke, Reilly, and Furman (39) reported the coulometric determination of iron using a solution volume of 5 ml., platinum indicator electrodes, and electrolytically generated ceric ion at a current rate of 50 microamps (5.0×10^{-10} equiv./sec.). The minimum amount of iron reported was 2.5×10^{-9} equiv., determined with an accuracy of 14.0%.

Furman and Cooke (40) developed the coulometric titration of vanadium employing a solution volume of 60 ml., platinum indicator electrodes, and electrolytically generated ferrous ion titrant at a current rate of 2.0 milliamps (2.0×10^{-8} equiv./sec.). The minimum quantity of vanadium reported was 1.2×10^{-7} equiv., determined with an accuracy of 3.5%.

Deford, Johns, and Pitts (41) investigated the coulometric determination of hydrochloric acid and sodium hydroxide using a glass indicator electrode, a solution volume of 150 ml., and externally generated hydrogen and hydroxyl ions at the current rate of 100 milliamps (1.0×10^{-6} equiv./sec.). The minimum amounts of hydrochloric acid and sodium hydroxide reported were 1.2×10^{-3} equiv., determined with an accuracy of 0.20%.

Lingane (42) reported the determination of lead, copper, and bismuth by electro-deposition at a mercury cathode at a potential of -0.50 volts. The solution volume was 100 ml. and a constant current of 50 milliamps (5.0×10^{-7} equiv./sec.) was applied. The minimum amount of lead reported was 4.0×10^{-4} equiv., determined with an accuracy of 1.0%. Copper and bismuth were similarly determined in a solution volume of 50 ml. The minimum amount of copper reported was 1.9×10^{-4} equiv., determined with an accuracy of 5.0%. The minimum quantity of bismuth reported was 1.4×10^{-4} equiv., determined with an accuracy of 7.0%.

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(39) W. D. Cooke, C. N. Reilly, & N. H. Furman, Ibid, 23, 1662 (1951)
(40) N. H. Furman & W. D. Cooke, Ibid, 23, 1665 (1951)
(41) D. D. Deford, C. J. Johns, & J. N. Pitts, Ibid, 23, 941 (1951)
(42) J. J. Lingane, "Electro-analytical Chemistry", Interscience Publishers, N.Y., 1953, pp. 357-365

Chloride, bromide, and iodide were also determined via electrodeposition by Lingane (42) using a controlled potential silver plated platinum anode and a solution volume of 25 ml. The minimum amount of chloride reported was 6.5×10^{-6} equiv., determined with an accuracy of 4.0%. The minimum amount of bromide reported was 6.3×10^{-6} equiv., determined with an accuracy of 2.0%. The minimum amount of iodide reported was 3.9×10^{-6} equiv., determined with an accuracy of 8.0%.

MacNevin and Baker (43) investigated the analysis of iron and arsenic via electro-oxidation at a controlled potential anode. A solution volume of 100 ml. and a platinum anode were used. The minimum quantity of iron and arsenic reported was 2.5×10^{-4} equiv., determined with an accuracy of 2.5%.

Brown and Swift (44) described the coulometric titration of antimony using an initial solution volume of 50 ml. and electrolytically generated bromine at a current rate of 1.0 milliamps (1.0×10^{-8} equiv./sec.). The minimum quantity of antimony reported was 1.6×10^{-7} equiv., determined with an accuracy of 10.0%.

Wooster, Farrington and Swift (45) determined iodide coulometrically in a solution volume of 50 ml. using electrolytically generated bromine at current rate of 1.0 milliamps (1.0×10^{-8} equiv./sec.). The minimum quantity of iodide reported was 7.9×10^{-8} equiv., determined with an accuracy of 2.0%.

Buck, Farrington, and swift (46) described the coulometric titration of thallium with electrolytically generated bromine at current rate of 1.0 milliamps (1.0×10^{-8} equiv./sec.). in a solution volume of 40 ml. The minimum amount of thallium reported was 8.8×10^{-7} equiv., determined with an accuracy of 0.2%.

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(43) W. MacNevin & B. Baker, Anal. Chem., 24, 986 (1952)
(44) R. Brown & E. H. Swift, J. Amer. Chem. Soc., 71, 2717 (1949)
(45) W. Wooster, P. S. Farrington, & E. H. Swift, Anal. Chem. 21, 1457 (1949)
(46) R. Buck, P. S. Farrington & E. H. Swift, Ibid, 24, 1195 (1952)

The coulometric analysis of aniline was developed by Buck and Swift (47) using electrolytically generated bromine at current rate of 1.0 milliamps (1.0×10^{-8} equiv./sec.) and initial volume of 45 ml. Since the bromination of aniline proceeds slowly, an excess of bromine was generated and then back titrated with the generation of cuprous ion. The minimum quantity of aniline reported was 7.7×10^{-7} equiv., determined with an accuracy of 2.0%.

Ramsey, Farrington, and Swift (48) reported the coulometric titration of arsenic with electrolytically generated iodine at a current rate of 1.0 milliamp (1.0×10^{-8} equiv./sec.) in a volume of 50 ml. The minimum quantity of arsenic reported was 1.9×10^{-6} equiv., determined with an accuracy of 0.20%. The calculated minimum limit is 5.0×10^{-9} equiv.

Carson and Ko (49) developed the coulometric analysis of weak organic acids using electrolytically generated hydroxyl ion at a platinum cathode with a current rate of 3.0 milliamps (3.0×10^{-8} equiv./sec.), and a solution volume of 5 ml. A glass electrode served as the indicator electrode. The minimum amount of acetic acid reported was 8.4×10^{-7} equiv., determined with an accuracy of 2.0%.

C. Conclusions:

This discussion of the coulometric technique has shown that the practical limit of sensitivity of this method has been fully realized in several instances, and that determinations of amounts of material of the order of 10^{-10} equivalents or less are not uncommon. This is a very considerable improvement in sensitivity over any other presently available electroanalytical technique.

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(47) R. Buck & E. H. Swift, Anal. Chem., 24, 499 (1952)
(48) W. Ramsey, F. S. Farrington, &. E. H. Swift, Ibid, 22, 332 (1950)
(49) W. N. Carson & R. Ko, Ibid, 23, 1019 (1951)

A summary of the work done in the field of coulometry as previously discussed is given in Table III.

TABLE III

Material	Minimum Amt. Reported (equivalents)	Per Cent Accuracy	Reference
Antimony	1.6×10^{-7}	10.0	(45)
Arsenic	8.0×10^{-7}	0.60	(29)
Bismuth	1.4×10^{-4}	7.0	(42)
Cerium	1.0×10^{-5}	0.60	(30)
Chromium	1.0×10^{-6}	1.0	(37)
Copper	1.9×10^{-4}	5.0	(42)
Iron	2.5×10^{-9}	14.0	(39)
Lead	4.0×10^{-4}	1.0	(42)
Manganese	2.7×10^{-10}	5.0	(34)
Silver	4.6×10^{-12}	20.0	(35)
Thallium	8.8×10^{-7}	0.20	(47)
Uranium	4.2×10^{-8}	8.0	(33)
Vanadium	1.2×10^{-7}	3.5	(40)
Chloride	6.5×10^{-6}	4.0	(43)
Bromide	6.3×10^{-6}	2.0	(43)
Iodide	7.9×10^{-8}	2.0	(46)
Hydrochloric Acid	1.2×10^{-3}	0.20	(41)
Sodium Hydroxide	1.2×10^{-3}	0.20	(41)
Acetic Acid	8.4×10^{-7}	2.0	(50)
Aniline	7.7×10^{-7}	2.0	(48)
8-Quinolinol	1.1×10^{-5}	0.50	(31)
Thiodiglycol	6.4×10^{-7}	2.0	(28)

VI. CONDUCTIMETRIC TITRATIONS OF TRACE AMOUNTS

A. Alternating Current Methods:

The conductimetric titration is usually carried out in a cell fitted with platinum electrodes and changes in conductance of the solution during the titration are measured via a Wheatstone bridge circuit arrangement. A plot is made of the conductance (bridge unbalance current) against the volume of titrant added and the end point is generally determined as the point of intersection of two more or less straight lines drawn through the experimentally determined points.

In the following discussion of some of the many successful conductimetric determinations reported in the literature, the present writer has in each case calculated the theoretical maximum sensitivity using the experimental conditions given in the reports and also employing the following arbitrary assumptions concerning practical instrucmental limitations.

a) The smallest increment of titrant deliverable with 1% accuracy is taken 1 lambda (10^{-3} ml.).

b) The smallest total increase in conductance that can serve to define a straight line with an accuracy of 1-5% is taken as 0.10 micro-amp, or the equivalent in micro mhos.

To illustrate a typical calculations, we may consider the titration of sulfate ion with 0.20 M barium nitrate in an initial volume of 500 ml. Experimental data (50) shows that an increase of 10.0 micro-amps in solution conductance results from the addition of 0.10 ml. of titrant beyond the end point. Employing the assumptions mentioned above, it is readily seen that 2 lambda of titrant (introduced as 1 lambda increments) would suffice to define a straight line beyond the end point. The minimum concentration of sulfate thus titrated may then be calculated from the known volume and strength of the titrant added and from the known initial volume of the sample. In this example, the maximum theoretical sensitivity is thus calculated to 8.0×10^{-7} M.

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(50) L. J. Anderson & R. R. Revelle, Anal. Chem., 19, 264 (1947)

Fig. 3 represents a hypothetical curve illustrating the above calculation.

The literature contains many reports of the successful use of the conductimetric technique in both macro and micro determinations, of which the following are typical examples:

Jander and Harms (51) reported the conductimetric determination of phosphate using 0.433 M bismuth perchlorate as the titrant and an initial volume of 40 ml. The titrant was standardized gravimetrically and the titration was carried out in the presence of perchloric acid. An increase of 5.0 microamps in conductance was noted upon the addition of 0.10 ml. of titrant beyond the end point. The minimum amount of phosphate reported was 6.3×10^{-3} M, determined with an accuracy of 0.5%. The calculated minimum concentration for these experimental conditions is 4.0×10^{-5} M.

Jander and Harms (52) developed the micro-titration of arsenic using as the titrant a solution of iodine in 99% alcohol. The titrant strength was 1.0×10^{-4} M and was obtained by both volumetric and conductimetric standardization. The initial solution volume was 3 ml. The minimum concentration of arsenic reported was 1.8×10^{-7} M, determined with an accuracy of 12.5%. The calculated minimum concentration for these experimental conditions is 7.0×10^{-8} M.

The conductimetric determination of perchlorate and iodide in the presence of large amounts of foreign electrolytes and described by

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(51) G. Jander & J. Harms, Z. Angewandte Chem., 49, 106 (1936)
(52) G. Jander & [illegible]. Harms, Z. Angewandte Chem., 48, 267 (1935)

Jander and Ebert (53). The titrant for the perchlorate analysis was 0.182 M barium hydroxide and the initial volume was 35 ml. An increase of 4.2 micro-amps in conductance resulted from the addition of 0.10 ml. of titrant beyond the end-point. The minimum concentration of perchlorate reported was 6.0×10^{-4} M, determined with an accuracy of 2.0%. The calculated minimum for these experimental conditions is 3.1×10^{-5} M. The titrant for the iodide determination was 0.994 M silver nitrate and the initial volume was 35 ml. The addition of 0.10 ml. of titrant beyond the end point caused an increase of 15.3 micro-amps in conductance. The minimum concentration of iodide reported was 3.0×10^{-4} M, determined with an accuracy of 1.0%. The calculated minimum for these experimental conditions is 5.7×10^{-5} M.

Anderson and Revelle (54) reported the macro and micro conductimetric determination of sulfate using silver electrodes and barium nitrate as the titrant. For the macro work, the initial volume was 500 ml. and the titrant was 0.208 M barium nitrate. An increase of 10.0 micro-amps in conductance was noted upon the addition of 0.10 ml. of titrant beyond the end point. The minimum sulfate concentration reported was 1.4×10^{-3} M, determined with an accuracy of 0.20%. The calculated minimum for these experimental conditions is 8.3×10^{-7} M. For micro work, the initial volume was 100 ml. and the titrant was 0.353 M barium nitrate. The addition of 0.10 ml. of titrant beyond the end point resulted in an increase of 180.0 micro-amps in conductance. The minimum sulfate concentration reported was 1.2×10^{-4} M, determined with an accuracy of 1.0%. The calculated minimum for these experimental conditions is 7.1×10^{-5} M.

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(53) G. Jander & A. Ebert, Z. Elektrochem., 41, 790 (1935)
(54) L. J. Anderson & R. R. Revelle, Anal. Chem., 19, 254 (1947)

Polsky, Betz, and Betz (55) reported the conductimetric determination of chloride, sulfate and calcium in water analysis. The procedure was to measure the conductance of the sample both before and after the addition of a reagent which completely precipitated the ion of interest. The concentration of the ion of interest was then obtained directly from a previously plotted standard curve of conductance versus concentration. The initial volume was 100 ml. and the precipitating agents for chloride, sulfate, and calcium were silver nitrate, barium chloride, and sodium oxalate respectively. The standard curve plots for both chloride and sulfate showed an increase in.conductance of about 2.0 micro-mhos for a 1 ppm increase in concentration of chloride or sulfate. No data was given for the standard curve plot of calcium ion. The minimum conductance measurable with standard commercial instrumentation was reported as 2.0 micro-mhos. The minimum concentration of chloride reported was 5 ppms, determined with an accuracy of 0.5 ppm. The minimum sulfate concentration reported was 8 ppm, determined with an accuracy of 0.5 ppm and the minimum calcium reported was 15 ppm, determined with an accuracy of 1.0 ppm. The calculated minimum for sulfate is 1.0 ppm.

Jander and Immig (56) carried out micro-conductimetric determinations of silver, lead, cadmium, copper, bismuth, and chloride. The initial volume for the micro-determinations of the metals was 40 ml. and the titrant used was 2.5 x 10^{-5} M hydrogen sulfide solution, standardized iodometrically. An average increase in conductance of 20.0 micro-amps resulted from the addition of 0.10 ml. of titrant beyond the end point in titration of the metals. The minimum concentration reported for the metals in general was 1.0 x 10^{-7} M, determined with an average accuracy of 6.0%. The calculated minimum for these experimental conditions is 1.1 x 10^{-9} M. For the microanalysis of chloride, the initial volume was 4 ml. with 96% ethanol serving as the solvent. The titrant was 1.0 x 10^{-3} M silver nitrate. An increase of 15.0 micro-amps in conductance resulted from the addition of 0.10 ml. of titrant beyond the end point. The minimum concentration of chloride reported was 7.0 x 10^{-6} M, determined with an accuracy of 12.0%. The calculated minimum for these experimental conditions is 5.0 x 10^{-7} M.

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(55) J. W. Polsky, W. H. Betz, & L. D. Betz, Ibid, 19, 657 (1947)
(56) G. Jander & H. Immig, Z. Elektrochem., 43, 207 (1937)

Jenson and Parrack (57) have reported the successful use of high frequency alternating current in the conductimetric determination of various susbstances. The principle involved is that any change in ionic conductance or dielectric constant of the solution results in a change in the oscillator output. The oscillator frequency was 15-20 megacycles. This method eliminates the need for electrodes and makes possible titration in both polar and non-polar media. Solvents such as methanol and benzene were used in addition to aqueous media. The titration of hydrochloric acid was accomplished with 0.10 M sodium hydroxide in a volume of 100 ml. The addition of 0.10 ml. of titrant beyond the end point resulted in a 5.0 micro-amp increase in conductance. The minimum concentration of hydrochloric acid reported was 0.025 M, determined with an accuracy of 0.20%. The calculated minimum for these experimental conditions is 4.0 x 10^{-6} M.

Phthalic acid was determined in acetone solution using 0.10 M sodium methylate as the titrant and an initial volume of 100 ml. A conductance increase of 40.0 micro-amps resulted from the addition of 0.10 ml. of titrant beyond the end point. The minimum concentration of phthalic acid reported was 0.013 M, determined with an accuracy of 0.10%. The calculated minimum for these experimental conditions is 2.0×10^{-6} M.

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(57) F. W. Jensen & A. L. Parrack, Ind. & Eng. Chem., Anal. Ed., 18, 595 (1946)

Sodium carbonate was titrated with 0.10 M hydrochloric acid in a volume of 100 ml. A conductance increase of 0.50 micro-amps followed the addition of 0.10 ml. of titrant beyond the end point. The minimum concentration of sodium carbonate reported was 0.013 M, determined with an accuracy of 0.20%. The calculated minimum is 4.0×10^{-5} M.

Potassium chloride was determined by titration with 0.10 M silver nitrate in a volume of 100 ml. The addition of 0.10 ml. of titrant beyond the end point produced a 4.0 micro-amp increase in conductance. The minimum concentration of potassium chloride reported was 0.025 M, determined with an accuracy of 0.10%. The calculated minimum for these experimental conditions is 6.0×10^{-6} M.

Phosphoric acid was titrated with 0.10 M sodium hydroxide in a volume of 100 ml. A conductance increase of 4.0 micro-amps resulted from the addition of 0.10 ml. of titrant beyond the end point. The minimum concentration of phosphoric acid reported was 0.008 M, determined with an accuracy of 0.20%. The calculated minimum for these experimental conditions is 6.0×10^{-6} M.

Ferrous ammonium sulfate was determined by titration with 0.02 M potassium permanganate in a volume of 100 ml. The addition of 0.10 ml. of titrant beyond the end point resulted in an increase of 3.0 micro-amps in conductance. The minimum concentration of ferrous ammonium sulfate reported was 0.025 M, determined with an accuracy of 0.10%. The calculated minimum for these experimental conditions is 1.2×10^{-6} M.

Benzoic acid was titrated with 0.10 M sodium methylate using benzene as the solvent and a volume of 100 ml. A conductance increase of 5.0 micro-amps resulted from the addition of 0.10 ml. of titrant beyond the end point. The minimum concentration of benzoic acid reported was 0.025 M, determined with an accuracy of 0.10%. The calculated minimum for these experimental conditions is 4.0×10^{-6} M.

B. Direct Current Methods:

Taylor and Furman (58) have reported the successful adaptation to analytical purposes of the constant current conductance titration. Their investigations show that this new technique gives results as accurate as, and probably potentially more sensitive than those obtained by the standard A. C. conductance method. Direct current conductance is based upon the principle that if a constant direct current were passed across a solution through a pair of platinum primary electrodes, the voltage drop across a pair of tungsten secondary electrodes should be inversely proportional to the conductance of the solution. This conclusion was verified experimentally. Since this technique is less well-known than those previously discussed, the experimental conditions will be described in some detail.

The constant current source was a 540 volt battery in series with a veriable high resistance. The voltage drop across the pair of secondary tungsten electrodes was measured with a pH meter. The usual conductance curves were obtained by plotting the reciprocal of the voltage drop against the volume of titrant.

Fig. 4 illustrates schematically the electrical circuit for the direct current conductance titration.

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(58) R. P. Taylor & N. H. Furman, Anal. Chem., 24, 1931 (1952)

The titration procedure is as follows:

The sample is diluted to a volume of 100 ml. in the conductance cell. The switch is closed and the variable resistances are adjusted until the pH meter reads on the 700 mv scale. This resistance setting remains fixed throughout the titration. The switch is then opened, titrant is added from a 10 ml. burette in increments of 1 ml., and the switch is closed after the addition of each increment so that a voltage drop measurement may be made. A plot of the reciprocal voltage drop versus the volume of titrant added is then made to determine the end point.

Calculation of the maximum theoretical sensitivity of a direct current titration may be accomplished by employing the experimental conditions given in the literature report and also the following arbitrary assumptions:

a) The smallest increment of titrant deliverable with 1% accuracy is 1 lambda.

b) The smallest total increase in conductance that can serve to define a straight line with 1-5% accuracy is 0.1 milli-volt.

As an illustration, we may consider the titration of silver nitrate with 0.04 M sodium chloride in a volume of 100 ml. Experimental data (59) shows an increase of 10 mv in conductance upon the addition of 0.10 ml. of titrant beyond the end point. Employing the assumptions outlined above, it can be seen that 0.002 ml. of titrant (introduced as increments of 0.001 ml.) would suffice to define a straight line after the end point. The minimum concentration of silver nitrate thus titrated may then be calculated from the known volume and strength of the titrant and the initial volume of solution. In this instance, the maximum sensitivity is calculated to be 8.0×10^{-7} M.

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(59) Idem., Ibid., p. 1933

Taylor and Furman carried out a number of titrations according to the constant current technique, of which the following are typical:

Hydrochloric acid was titrated with 0.20 M sodium hydroxide in a volume of 100 ml. A conductance increase of 5 mv resulted from the addition of 0.10 ml. of titrant beyond the end point. The minimum concentration of hydrochloric acid reported was 1.3×10^{-4} M, determined with an accuracy of 0.10% The calculated minimum for these experimental conditions is 8.0×10^{-6} M.

Perchloric acid in glacial acetic solution was titrated with 0.10 M aniline acetate in a volume of 100 ml. A conductance increase of 33 mv was noted upon the addition of 0.10 ml. of titrant beyond the end point. The minimum concentration of perchloric acid reported was 6.6×10^{-4} M, determined with an accuracy of 0.30%. The calculated minimum for these experimental conditions is 6.0×10^{-7} M.

Silver nitrate was titrated with 0.04 M sodium chloride in a volume of 100 ml. The addition of 0.10 ml. of titrant beyond the end point resulted in an increase of 10 mv in conductance. The minimum concentration of silver nitrate reported was 5.4×10^{-5} M, determined with an accuracy of 0.10% The calculated minimum for these experimental conditions is 8.0×10^{-7} M.

The following table is a summary of the work done in the field of conductimetry as previously discussed:

TABLE IV

Material	Minimum Conc. Reported (Moles /Liter)	Per Cent Accuracy	Minimum Conc. Calculated (Moles / Liter)	Reference
Arsenic	1.8×10^{-7}	12.5	7.0×10^{-8}	(52)
Bismuth	1.0×10^{-7}	7.0	1.1×10^{-9}	(56)
Cadmium	1.0×10^{-7}	10.0	1.1×10^{-9}	(56)
Calcium	4.0×10^{-4}	7.0	No Data	(55)
Copper	1.0×10^{-7}	5.5	1.1×10^{-9}	(56)
Iron	5.0×10^{-3}	0.10	2.4×10^{-7}	(57)
Lead	1.0×10^{-7}	7.0	1.1×10^{-9}	(56)
Silver	1.0×10^{-7}	1.7	1.1×10^{-9}	(56)
Carbonate	8.0×10^{-3}	0.20	2.4×10^{-5}	(57)
Chloride	7.0×10^{-6}	12.0	5.0×10^{-7}	(56)
Iodide	3.0×10^{-4}	1.0	5.7×10^{-5}	(53)
Perchlorate	6.0×10^{-4}	2.0	3.1×10^{-5}	(53)
Phosphate	6.3×10^{-3}	0.50	4.0×10^{-5}	(51)
Sulfate	8.0×10^{-5}	6.0	1.0×10^{-5}	(55)
Benzoic Acid	2.5×10^{-2}	0.10	4.0×10^{-6}	(57)
Phthalic Acid	1.3×10^{-2}	0.10	2.0×10^{-6}	(57)

C. Conclusions:

Conductimetric methods appear to be limited at the trace level to concentrations of the order of 10^{-7} M to 10^{-9} M, at best. This is a considerable improvement in sensitivity over amperometric techniques, though not quite as sensitive as coulometry. Several of the investigators discussed have come quite close in practice to the calculated lower limit of sensitivity.

It is interesting to note that, in principle, A.C. conductimetry becomes less accurate as the concentration (and conductance) of the sample becomes very small, due to capacitance effects and dielectric losses. However, D.C. conductimetry is not affected by those factors, and hence may be ultimately capable of refinement to a much greater degree of sensitivity than the A.C. technique.

VII. The Field of Electronic Detection Techniques

A number of techniques exist in which the pressure of an atmospheric contaminant is detected directly in the gas phase by measuring the nature and/or number of excited or ionized species produced under conditions of constant excitation. The excitation may be produced through the agency of a radioactive source, a flame, a thermionic emitter, a radio-frequency discharge, an ultraviolet lamp, or other form of energy transducer. The field has grown rapidly in recent years under the impetus of developments in gas chromatography.

The question to be examined in this report is whether the potential practical sensitivity limits of these detection techniques are sufficiently low to justify a major effort in seeking ways and means of adapting and adjusting one of these detectors to the specific problem of responding to chemical agents of a given type without suffering interference from other atmospheric constituents.

It will be useful to start with a general discussion of the characteristics and parameters of gas chromatographic detectors as a class.

A. Detector Properties

The response of a detector, which is the read-out signal that measures the quantity of the component of interest, is generally a simple function of the number of vapor molecules that differ from the background (or carrier) gas, and is not usually sensitive to the kind of these molecules. For gas chromatography, the response of the detector should be a linear function of the concentration of the sensed species. The detector response should be continuous, predictable, and reproducible in responding to changes in the composition of the atmosphere flowing over it, and should not show hysteresis or memory effects. The detector should obey a physical law that permits the response to be read out as an electrical signal, suitable for amplification and presentation on automatic, continuous recording instrumentation. The response time of the detector should be rapid.

1. Response Time. The response time observed with a detector will depend upon the actual speed of response of the sensing element or process involved, the volume of the detector and its housing, the gas flow rate through the detector, and the time delays introduced in the associated electronic circuitry.

The internal (or, dead) volume of a detector affects the response because of the mixing which occurs, in this volume, of the sensed component and the carrier gas. This is an important effect in gas chromatography, because of the role it plays in modifying the shape of an elution peak, but it would not be important in gas analysis when the component of interest is dispersed in a volume of gas that is large compared with the volume of the detector. The detector volume should be 1/30 th of the volume of the gas sample containing the constituent to be sensed (60). Given this condition, the greater the detector volume, the greater will be the detector output for a given sample concentration, since there will be more sample in the detector at any instant, the greater the volume. This does not necessarily mean, however, that a greater sensitivity of detection will be achieved, since the noise and background signals may increase proportionately. At present, the largest detection dead volumes used are those found in the beta-ray detectors, and approximate 3 ml.

2. Sensitivity. The observed sensitivity of a detector is a function of the physical law obeyed by the device, the voltage sensitivity of the readout instrument, the flow rate and mixing characteristics of the constituent

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(60) I. G. McWilliam, J. Appl. Chem., 9, 379 (1959).

and the air stream. The ultimate sensitivity is often determined by the degree to which the background signal due to the carrier gas can be attenuated.

Some detectors give a signal that is related to the mass of the sensed component, whereas others give signals that are related to the concentration. The transfer function of the detector may be linear in some cases; exponential in others. This diversity in characteristics has led to a diversity of functions for expressing the sensitivity of detectors. Parameters that are often employed include: (a) minimum detectable sample size, (b) minimum detectable concentration, (c) minimum change in concentration which gives a change in signal equal to the background noise, (d) the Dimbat factor (61) $S = A.C_1 \cdot C_2 \cdot C_3/W$ where S is the sensitivity parameter in Cm^3 mV/mg, A is the area of the elution peak on a recorder chart in Cm^2, C_1 is the reciprocal of the chart speed of the recorder in min/cm, C_2 is the scale of the recorder in mV/cm, C_3 is the flow rate of carrier gas through the measuring cell in cm^3/min, and W is the weight of the sensed component in mg. (This sensitivity parameter, divided by background signal in microvolts, is equivalent to the gas concentration sensitivity in micrograms/microliter (62).

It has been pointed out (63) that the sensitivity parameter, S, is inapplicable to detectors whose response is related to the rate of mass input of the sensed compound, as is the case for the flame and argon detectors.

For ionization detectors, Lovelock (64) has proposed the "apparent ionization efficiency" as a sensitivity parameter, based on the total charge collected by the electrodes during the passage of 1 mole of the sensed substance through the detector. For detectors whose response is related to vapor concentration, this unit varies inversely with the rate at which the sample is passed through the detector.

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(61) M. Dimbat, P. E. Porter, and F. H. Stross, Anal. Chem., 28, 290 (1956)
(62) I. G. McWilliam, J. Appl. Chem., 9, 379 (1959)
(63) L. Ongkichong, "Gas Chromatography", R. P. Scott, editor, Butterworths, London, 1961
(64) J. E. Lovelock, Anal. Chem., 33, 162 (1961)

The limit of detection of a given sensor may be defined as the minimum weight of compound which can be determined with a specified statistical reliability. A limit or maximum sensitivity datum has no significance unless the statistical criterion is specified (65). The sensitivity of the detector itself does not measure the limit of detection passible with this detector, for the latter depends upon the magnitude of the background noise.

B. Types of Detectors

The following types of detectors are in use in gas chromatographic instrumentation.

1. Mass Proportional. In these detectors the output is the same for equal masses of all sensed components. An example is the beta-ray detector with hydrogen as the carrier gas. Thermal conductivity detectors with helium or hydrogen as the carrier gas are approximately mass proportional sensors.

2. Molecule Number Proportional. In these detectors the output is the same for equal numbers of molecules of all sensed components. An example of this class is the beta-ray detector with argon as the carrier gas.

3. Elemental Composition Proportional. The output of these detectors is proportional to the total number of atoms of a given kind in the specimen regardless of the form of combination of these atoms into molecules. An example is the CO_2 combustion detector, in which organic molecules are oxidized to yield CO_2 and other products, and the CO_2 is sensed. Under some conditions

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(65) H. W. Johnson and F. H. Stross, Anal. Chem., 30, 1586 (1958)

the flame ionization detector falls in this category.

4. Physical Property Proportional. The output of these detectors is proportional to some extensive property of the substance entering the chamber. An example is the flame temperature detector, in which the signal is related to the product of number of molcules entering the flame times the heat of combustion per molecule.

5. Empirical. In this class of detectors, the relationship between sample properties and sensor output is not simple enough, or sufficiently controlled, to permit direct, a priori correlations and calibrations to be made. Examples are the gas discharge detector, the emissivity detector, and the surface potential detector.

The following sections discuss those detectors which seem to be particularly relevant to the problems of the Chemical Corps.

VIII. The Surface Potential Detector

A small amount of thermionic emission occurs from the surfaces of all substances at all temperatures, the actual magnitude of the effect depending upon the nature of the substance and its temperature. If two dissimilar metals are connected together, the difference in emissions from their surfaces will cause the one emitting the smaller number of electrons to acquire a negative charge relative to the other until this contact potential difference builds up a gradient sufficient to cause the two emissions to become equal.

If now the surface of one of these metals is changed in some way, such as by the adsorption of vapor molecules, the contact potential difference will be altered. These potentials are best measured by means of the vibrating reed electrometer (66). In this device, the two metal plates form a capacitor, one plate of which is caused to vibrate. This generates an ac signal that is proportional in magnitude to the potential difference between the metal plates. The EMF is best measured by applying a bias voltage to the plates sufficient to reduce the ac signal to zero. The passage of an adsorbable vapor into this detector results in potential charges that are amplified and recorded.

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(66) C. Phillips, J. Sci. Instr., 28, 342 (1951); J. Griffiths, D. James and C. Phillips, Analyst, 77, 897 (1952); J. Griffiths and C. Phillips, J. Chem. Soc., 3446 (1954).

It has been observed that the sensitivity to vapors can be considerably increased if one of the plates is coated with a layer of a fatty acid or of collodion. The response of this detector is structure sensitive; in one form of this device positive signals were observed for esters and ethers, zero signals for non-polar substances, and negative signals for chlorinated compounds.

The sensitivity has been reported to be very high for polar vapors, increasing with increase in the molecular weight. Practical sensitivities as high as 1 mole of substance per 10^6 moles of carrier gas have been reported. However, the response tends to be slow, and non-linear, and marked memory effects are evident. For some substances, the response is irreversible. The signal is not readily related to the composition and concentration of the sample.

Conclusions. The contact potential detector is, in principle, an attractive possibility for the very sensitive detection of polar, non-volatile constituents in the presence of large excesses of the normal atmospheric components. However, the technique of making, surface-treating, and handling the vibrating capacitor surfaces need much improvement before this detector will be practical for the problems of the Chemical Corps.

IX. The Gas Density Balance

The gas density balance is an ingenious device for the detector of small density charges in a flowing gas. A typical construction is shown in Figure 5. The detector consists of a network of non-horizontal channels in a balanced bridge arrangement, similar in principle to the Wheatstone bridge. In this network, two points can be found, vertically displaced from one another, where the pressure difference is independent of the rate of flow of the gas. It is possible to combine two such networks in one of which the carrier gas flows (or, for Chemical Corps purposes, air from which the compound to be sensed has been removed), and in the other of which the carrier gas plus sample flows. The unbalance of these combined networks, or bridge circuit, is due only to any density difference between the two gases, and is independent of differences in the flow rates. This unbalance is measured by means of a differential thermocouple anemometer.

As shown in the Figure, the gas to be tested enters at I and divides upwards and downwards into two approximately equal streams. The reference gas enters at II, and also splits into two approximately equal streams, and then combines with the test gas stream, emerging at the common outlet III. The zero point is determined by allowing the same gas to flow into the two inlets, and adjusting the rods BCDE until the points X and Y are at exactly the same pressure. The sensor is the anemometer located in the center of the passageway XY. This anemometer contains a small electrically heated filament (hairpin heater, H), mounted equidistant from the ends of a two sections of copper wire, XJ_1 and J_2Y which are joined by a short length of constantan wire, J_1J_2, so as to form the two thermocouple junctions J_1 and J_2.

By rotating the anemometer, the temperatures of the junctions J_1 and J_2 can be exactly equalized. Any movement of gas through the passage XY will then be detected as a change in temperature of the two junctions. The thermal EMF is fed to a D.C. amplifier, and recorded on a self-balancing potentiometer (67).

Sensitivities of 1 molecule of sample per 10^4 to 10^5 molecules of carrier gas have been reported (68). The stability of the signal is very good if the rate of gas flow is not too great. The response is very linear over a wide concentration range, and is proportional to the difference in effective molecular weight between the sample and reference gases. Over a 30-minute period, a typical noise level is ±0.05 micro-volts with a drift of less than 0.3 micro-volts.

Other designs of this type of detector have been described by several workers (69), and commercial instruments based on these principles are available from Beckman Instruments, Fullerton, Calif.; Gow-Mac Instrument Co., Madison, N. Y.; Griffin and George, Ealing Road, Alperton, Middlesex, England; and Casella and Co., Regent House, Fitzroy Square, London, England.

Conclusions

The gas density balance would appear to be attractive for consideration by the Chemical Corps because of its high sensitivity coupled with excellent stability. Its practical application to chemical agent detection would require an investigation of techniques of employing the atmosphere being sampled to provide the agent-free reference gas for the detector.

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(67) A. J. P. Martin and A. T. James, Biochem. J., 63, 138 (1956); J. C. Hawkes in "Vapor Phase Chromatography," D. H. Desty, editor, Butterworths, London, 1957, p. 266; R. L. Pecsok, "Principles and Practice of Gas Chromatograph, "Wiley, N. Y., 1959, p. 118.

(68) C. W. Munday and G. R. Primavesi, in "Vapor Phase Chromatography" D. H. Desty, editor, pp. 266.

(69) W. J. Murray, Austr. J. Appl. Sci, 10, 156 (1959); A. J. P. Martin and J. C. Winters, Anal. Chem., 31, 1954 (1959); A. G. Nerheim, Anal. Chem., 32, 42A, (1960).

X. Flame Temperature Detector

If hydrogen is used as the carrier gas, and is burned at a suitable orifice, the temperature of the flame is observed to be sensitive to the pressure of other constituents. (70)

An iron-constantan thermocouple of 32 S.W.g. wires is mounted slightly above the flame issuing from a jet made of 0.2 mm Pyrex capillary tubing; both parts are rigidly mounted, and the flame is protected from drafts by a baffle system. Wirth (71) has found some improvement in baseline stability if a hypodermic needle tip is employed for the jet.

The sensitivity of detection of hydrocarbons has been reported as 0.07 micrograms per milliliter with a signal-to-noise ratio of 4:1. The detector is simple, convenient, has a rapid speed of response, and is fairly linear. However, it is difficult to realize the full sensitivity because of a tendency toward instability; the flow rate of gas into the flame must be very carefully controlled. This detector is relatively non-selective.

Conclusions

The problem of selectively removing all combustible gases from an air stream without removing any chemical agents that may be present appears to be insuperable. In the absence of this expedient, it would appear that the potential high sensitivity of the flame temperature detector cannot be utilized for the purposes of the Chemical Corps.

XI. Ionization Detectors

If ionization can be generated in a gas sample, the collection of the gaseous ions at a suitable electrode pair can provide a sensitive quantitative measure of the concentration of ionizable species in the sample.

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(70) R.P.W. Scott, Nature, 176, 793 (1955); "Vapor Phase Chromatography," D.H. Desty, editor, Butterworths, London, 1957, p. 131; B.A. Rose, Analyst, 84, 585 (1959).

(71) "Vapor Phase Chromatography," D.H. Desty, editor, Butterworths, London, 1957, p. 154.

At low ion densities, the properties of gaseous conductors are highly favorable for the collection of all of the ions liberated by the presence of the test gas. The ultimate limit of sensitivity of this technique depends upon (1) the efficiency of the presence of ionization employed; (2) the extent of interference arising from ionization of the carrier gas, and (3) the practical limitations of the equipment for measuring small currents.

Under perfect conditions, if all of the test gas and none of the carrier gas were ionized, we might expect to observe the presence of as little as 10-100 molecules of a substance. However, no detection method so far has succeeded in producing a background ionization of the carrier gas of less than 10^7 ion pairs per second, and none is able to ionize the test substance completely(72).

The principles and characteristics of the various detection techniques based upon the collection of an ionization current have recently been summarized by Lovelock (72) and, need not be repeated here. It will be sufficient to summarize the practical detection limits that have been found for the several techniques employing ionization.

Method	Minimum Detectable Conc. by volume
Cross Section Ionization	10^{-4}
Electron Mobility, Indirect	10^{-6}
Electron Mobility, Direct	10^{-8}
Flame Ionization	10^{-11}
Argon Detector	10^{-12}
Electron Capture	10^{-13}

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(72) J. E. Lovelock, Anal. Chem., 33, 162 (1961).

It is evident that certain of the ionization detection techniques have limits of detection that are not approached by any of the other methods. These methods are, however, circumscribed by certain limitations, chief among which are the difficulties of maintaining stable background currents and low noise levels.

Conclusions

The ionization detection techniques offer the possibility of such high sensitivities that it does not seem resonable to dismiss them for any presumed deficiencies. A method that is capable of a sensitivity of 10^{-13} ml. per ml. of carrier gas can afford to throw away a million-fold factor of sensitivity and still be more sensitive than most other methods.

The special problems of the Chemical Corps in utilizing one of the ionization techniques, will involve the minimizing of background and interferences without undue loss of the desired signal.

XII. Recommendations.

Of the detection techniques surveyed in this report, there are two that stand out as capable of far greater practical detection sensitivity than any others. These are (a) coulometry in moderate volumes of solution, and (b) direct gas phase ionization current measurement.

It appears that these techniques offer the greatest rewards for ingenious and skillful solutions to the chemical problems involved in achieving good resolution and specificity with respect to the chemical agents. A small breakthrough in sampling technique applied to classical detection methods will yield only a slight improvement in the limits of detection of agents; but a similar break-through applied to coulometry or ionization detection may mean pushing the limits of detection down by several orders of magnitude.

The break-throughs that are needed, then, are (a) chemical reactions that can convert the chemical agents into electrolyzable species with good efficiency, and without producing interfering substances from other atmospheric constituents, and (b) chemical or physical techniques of peaking the response of an ionization detector for the chemical agents, while discriminating against other atmospheric constituents.

The other detection techniques that have been treated in this report also offer interesting possibilities that should not be overlooked by the Chemical Corps.